

PART I. TOTAL SYNTHESIS OF (-)-CYCLOCLORENONE

PART II. TOTAL SYNTHESIS OF ( $\pm$ )- $\alpha$ -VETISPIRENE

A THESIS

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Paul Fredric Ingwalson

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## GLOSSARY OF ABBREVIATIONS

Anal.	C,H analysis
bp	boiling point
cm <sup>-1</sup>	wave numbers (ir spectrum)
DDHQ	2,3-dichloro-5,6-dicyano-p-hydroquinone
DDQ	2,3-dichloro-5,6-dicyano-p-benzoquinone
EMD	exact mass determination (mass spectrum)
eV	electron volt
glc	gas-liquid chromatography
Hz	Hertz (cycles per second, nmr spectrum)
ir	infrared
J	coupling constant (nmr spectrum)
M <sup>+</sup>	molecular ion (mass spectrum)
m/e	mass to charge ratio (mass spectrum)
mp	melting point
nm	nanometers (millimicrons, uv spectrum)
nmr	nuclear magnetic resonance
ppm	parts per million (nmr spectrum)
uv	ultraviolet
w <sub>h</sub>	width at half-height (nmr spectrum)
[α] <sub>D</sub>	specific rotation at sodium D line
ε	extinction coefficient (uv spectrum)



## SUMMARY

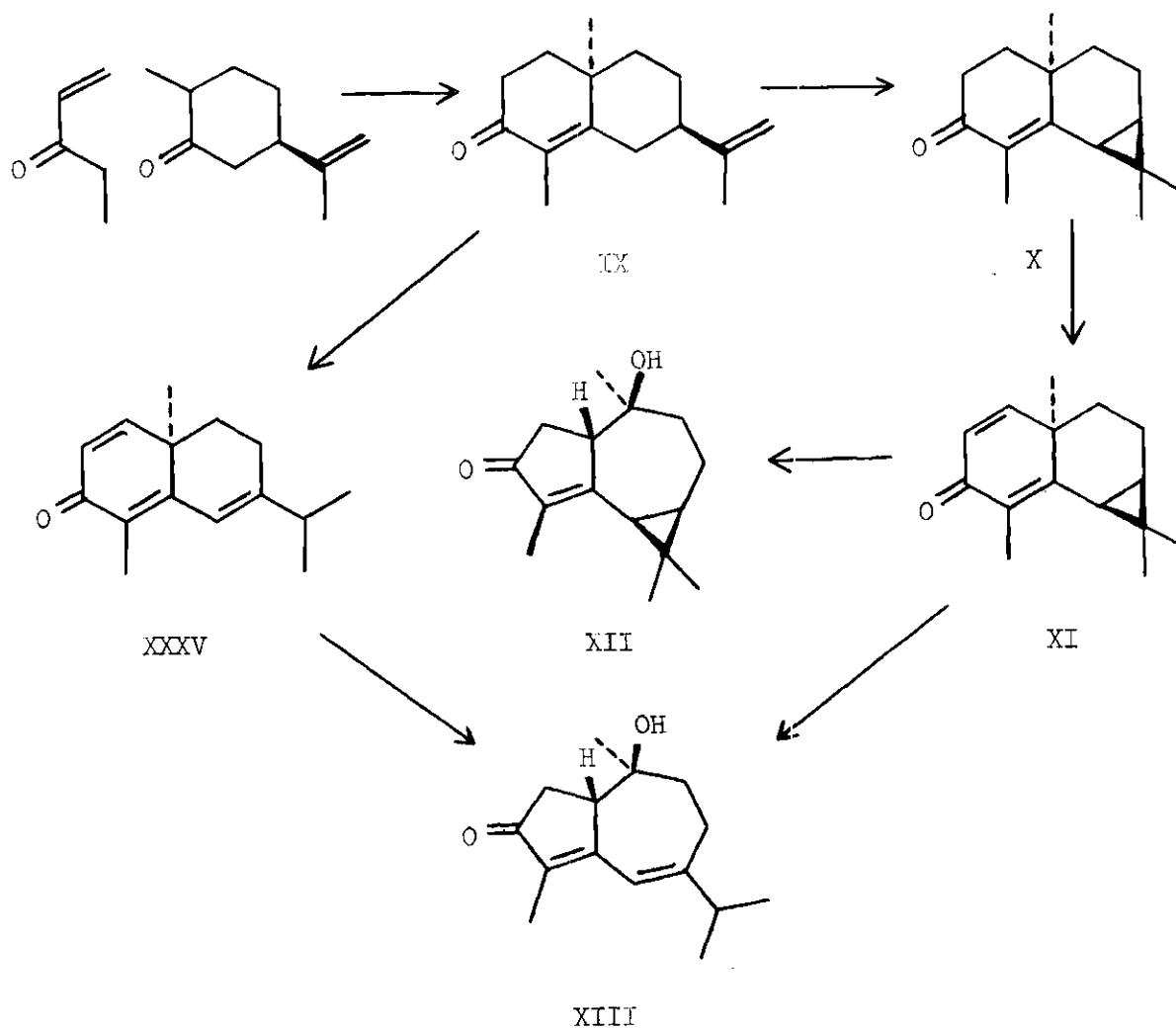
Part I

The principal goal of this research was to carry out a stereospecific synthesis of the sesquiterpene natural product (-)-cyclocolorenone (I). The key step in the synthesis involved the photochemical rearrangement of a 6/6-fused cross-conjugated cyclohexadienone to give 5/7-fused precursor to the natural product. As a result significant investigations were made into the photochemistry of cyclohexadienones containing a cyclopropyl ring which extends the conjugation of the enone system.

The condensation of ethyl vinyl ketone with (+)-dihydrocarvone and dehydration of the resulting ketol gave (-)-epi- $\alpha$ -cyperone (IX). The cyclopropyl ring was then closed in two steps to give (-)-maalienone (X), which was in turn oxidized to 1,2-dehydromaalienone (XI). Irradiation of XI in aqueous acetic acid was expected to give the 5/7-fused hydroxy enone XII, but it was found that the cyclopropyl dienone was stable to ultraviolet light. In a further attempt to rearrange XI benzophenone was used as a sensitizer. In this case the rearrangement took place, but the cyclopropyl ring was opened in the process to give the hydroxy dienone XIII as the only identifiable product.

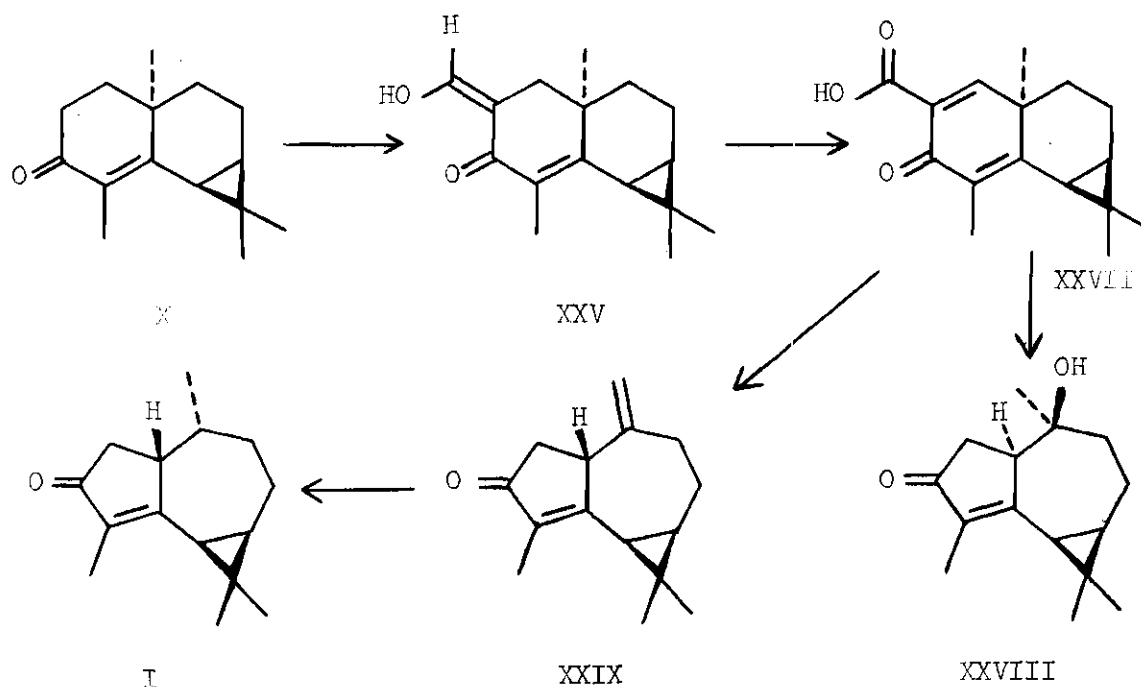
(-)-Epi- $\alpha$ -cyperone was isomerized to  $\beta$ -cyperone, which was in turn oxidized to 1,2-dehydro- $\beta$ -cyperone(XXXV). This trienone was

irradiated in the presence of benzophenone under the same conditions as the cyclopropyl dienone had been, and the same hydroxy dienone XIII was produced. It is possible, therefore, that XXXV was an intermediate in the rearrangement of XI. The opening of the three-membered ring made this an undesirable route to the natural product, and it was therefore necessary to choose another dienone for the photolysis.



Ethyl formate was condensed with (-)-maalienone to give the 2-hydroxymethylene derivative XXV. Oxidation resulted in the 2-formyl dienone, and further oxidation produced 2-carboxy-1,2-dehydromaalienone (XXVII). Irradiation in aqueous acetic acid gave a 5/7-fused hydroxy enone XXVIII with the cyclopropyl ring closed, but epimerization at C-1 had apparently taken place in the aqueous acid to give the undesired epimer with a  $1\alpha$ -hydrogen. Irradiation of the carboxy dienone in anhydrous dioxane yielded the 5/7-fused dienone XXIX, which not only had the three-membered ring intact but also had the desired  $1\beta$ -hydrogen.

Hydrogenation of the exocyclic double bond from the least hindered  $\beta$  face of the molecule produced (-)-cyclocolorenone and thus completed the synthesis.



## Part II

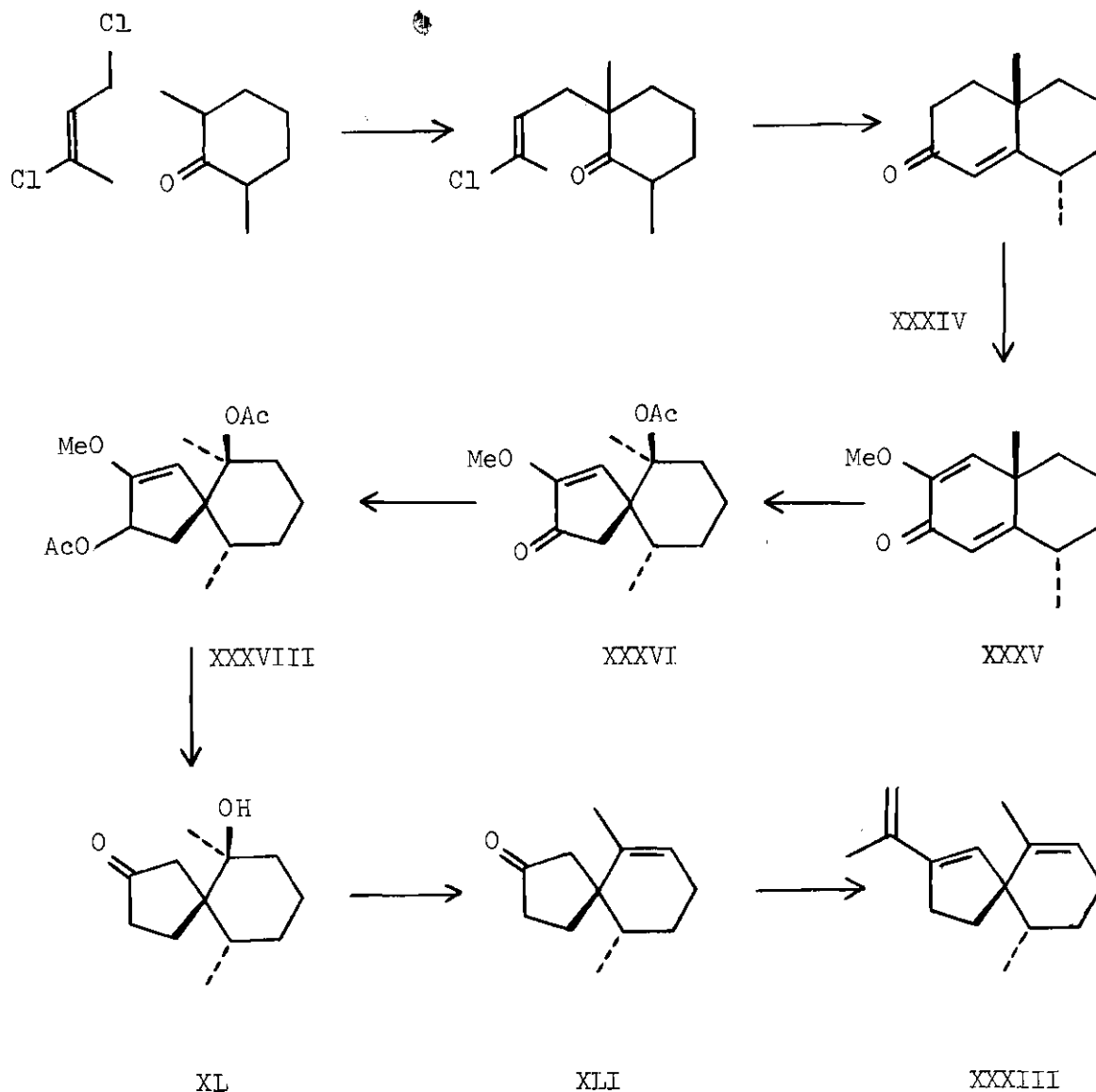
The principal goal of this research was to complete the synthesis of the sesquiterpene natural product  $\alpha$ -vetispiene (XXXIII). The key step in this synthesis involved the photochemical rearrangement of a 6/6-fused cross-conjugated cyclohexadienone to give a [4.5] spiro system which was a precursor to the natural product. A possible general route to vetispirane sesquiterpenes through a common intermediate was developed.

2,6-Dimethylcyclohexanone was alkylated with 1,3-dichloro-2-butene to give the chlorocrotyl ketone. In three steps the A ring was closed yielding 3-keto-6,10-dimethyl- $\Delta^4$ -octahydronaphthalene (XXXIV). This enone was oxidized to the 2-acetoxy derivative which was in turn hydrolyzed and oxidized to the 2-hydroxy dienone. Methylation gave 2-methoxy-3-keto-6,10-dimethyl- $\Delta^{1,4}$ -hexahydronaphthalene (XXXV) which had the necessary stereochemistry and substituents for conversion into a precursor of  $\alpha$ -vetispiene. The methoxyl group at C-2 served a dual purpose. As an electron donating group at C-2 it directed the rearrangement to give the spiro system rather than a 5/7-fused system. And it provided a method of obtaining, in a later step, a carbonyl group at C-2 and thus of introducing the necessary side chain.

Irradiation of the methoxy dienone in glacial acetic acid resulted in rearrangement to give the acetoxy ketone XXXVI. Reduction and subsequent acetylation of the resulting hydroxy acetate yielded the diacetate XXXVIII. This diacetate was reduced, and the enol ether function was hydrolyzed to give the hydroxy ketone XL.

Dehydration gave the key intermediate XLI. From this point it should be possible to produce several different vetispirane sesquiterpenes by introduction of suitable side chains at C-2.

The synthesis of  $\alpha$ -vetispirane was completed by addition of isopropenyl magnesium bromide to the carbonyl and dehydration to give the triene. Introduction of an acetyl group at C-2 would complete formal total syntheses of  $\beta$ -vetivone, hinesol, and agarospirol.

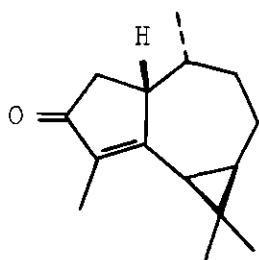


## PART I

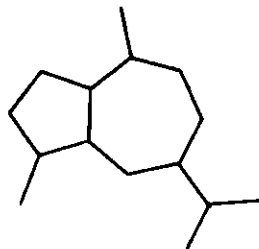
## CHAPTER I

## INTRODUCTION

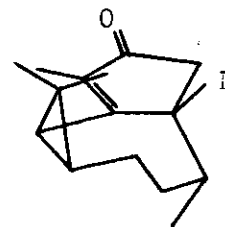
The sesquiterpene ketone (-)-cyclocolorenone (I) was first isolated from Pseudowintera colorata, a plant endemic to New Zealand, by Corbett and Speden (1). Extraction of the plant and distillation of the resulting oil yielded the natural product as the highest boiling constituent. Since then cyclocolorenone has been found in other plants, including Compositae species and goldenrod (2).



I



II



III

It has been established for some time that the ketone is  $\alpha,\beta$ -unsaturated and has a carbon skeleton related to that of guaiane (II) (1). The uv maximum of cyclocolorenone at 264 nm is at a longer wavelength than normal for an  $\alpha,\beta$ -unsaturated ketone due to the fact that the cyclopropyl ring extends the conjugated system. The sigma bonds in the three-membered ring are oriented in such a way as to

be almost parallel to the p orbitals of the conjugated system (III).

The relative and absolute stereochemistry of (-)-cyclocolorenone has been established by Büchi, Kauffman, and Loewenthal by consideration of its biosynthesis from all-trans-farnesol and subsequent synthesis of 1-epicyclocolorenone (IV) (3). The starting material for this synthesis was O-acetylphotosantonin acid lactone (VI) which was easily prepared by the photochemical rearrangement of  $\alpha$ -santonin (V). Acetic acid was first eliminated on treatment of VI with concentrated sulfuric acid, and the lactone function was hydrogenolized with chromous chloride to give the acid VII. Catalytic reduction of the 1,10-double bond from the  $\beta$  face of the molecule and modification of the C-7 side chain resulted in VIII. Closure of the three-membered ring might be expected to give the natural product, but it was found that successive treatment with hydrogen bromide in acetic acid and methanolic alkali caused epimerization of the 1-hydrogen and produced the more thermodynamically stable product IV. Epimerization of natural cyclocolorenone to give IV and consideration that the nmr absorption for the 10-methyl group in cyclocolorenone comes at relatively high field because it is shielded by the enone chromophore led Büchi to the conclusion that the cyclopropyl ring and the 1- and 10-hydrogens are all  $\beta$  in (-)-cyclocolorenone.

The purpose of this research was to synthesize natural, optically active cyclocolorenone. The route chosen to achieve this end involved the photochemical rearrangement of a 6/6-fused cross-conjugated cyclohexadienone of type A (see Chart II) to give a 5/7-fused enone



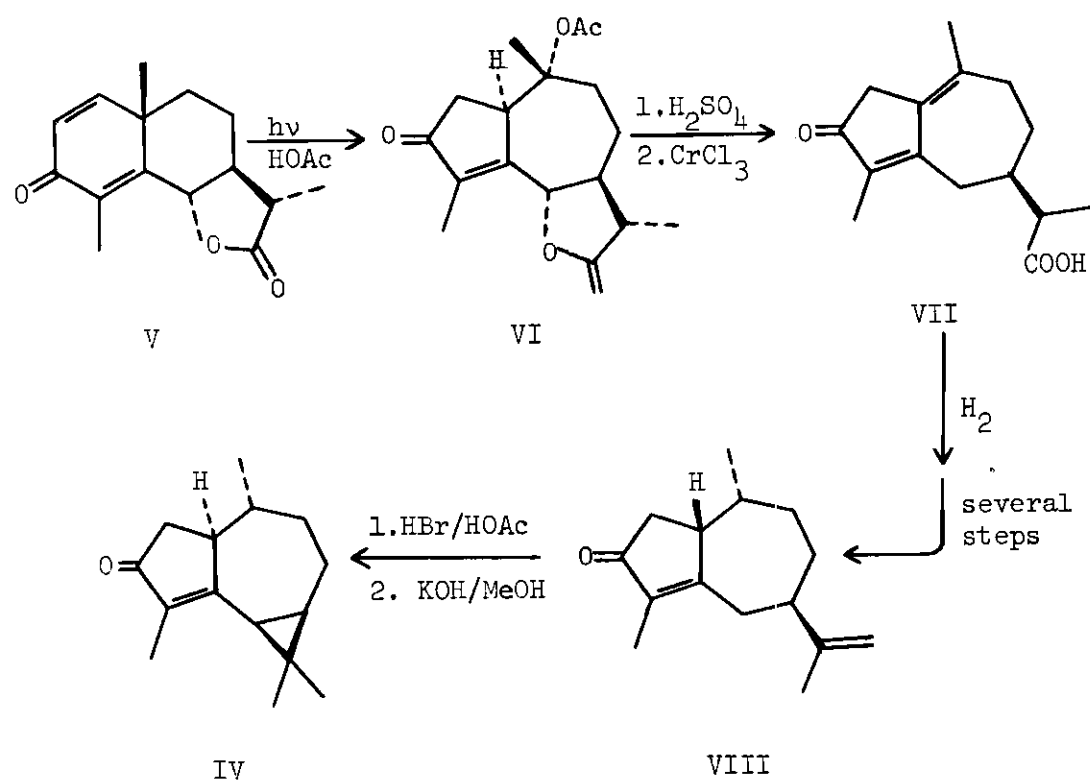
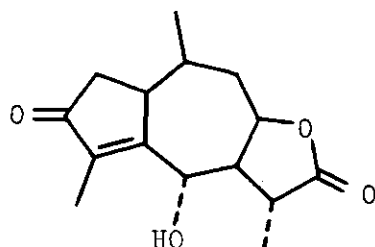
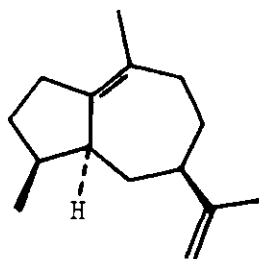
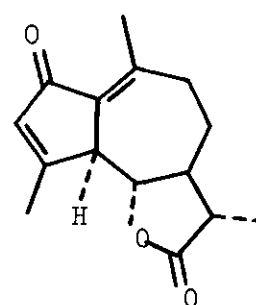


Chart I. Synthesis of 1-Epicyclocolorone.

of type B. Since Barton first studied the rearrangement of  $\alpha$ -santonin and elucidated some of the products (4), there has been a growing interest in the photochemistry of these dienones. It has been well documented that irradiations in aqueous acidic media produce varying yields of hydroxy enones of types B and C and that the rearrangements are stereospecific (5). A number of hydroazulenenic natural products have been synthesized utilizing the photochemical rearrangements of appropriate 6/6-fused cross-conjugated cyclohexadienones as the key synthetic steps. Among these are geigerin (6),  $\alpha$ -bulnesene (7), achillin and deacetoxymatricarin (8).



geigerin

 $\alpha$ -bulnesene

deacetoxymatricarin

According to the mechanism proposed by Zimmerman and coworkers (9) there is, in the rearrangement, an  $n \rightarrow \pi^*$  electronic transition to the singlet excited state of the dienone and intersystem crossing to give the triplet excited state. This is followed by 1,5-bonding to give a diradical which can be represented by resonance forms D and E.  $\pi^* \rightarrow n$  demotion and protonation results in the mesoionic species

represented by F and G. Depending on the electronic characteristics of the substituents  $R_1$  and  $R_2$ , either F or G is the more important resonance structure, and attack by solvent results in either enone B or enone C.

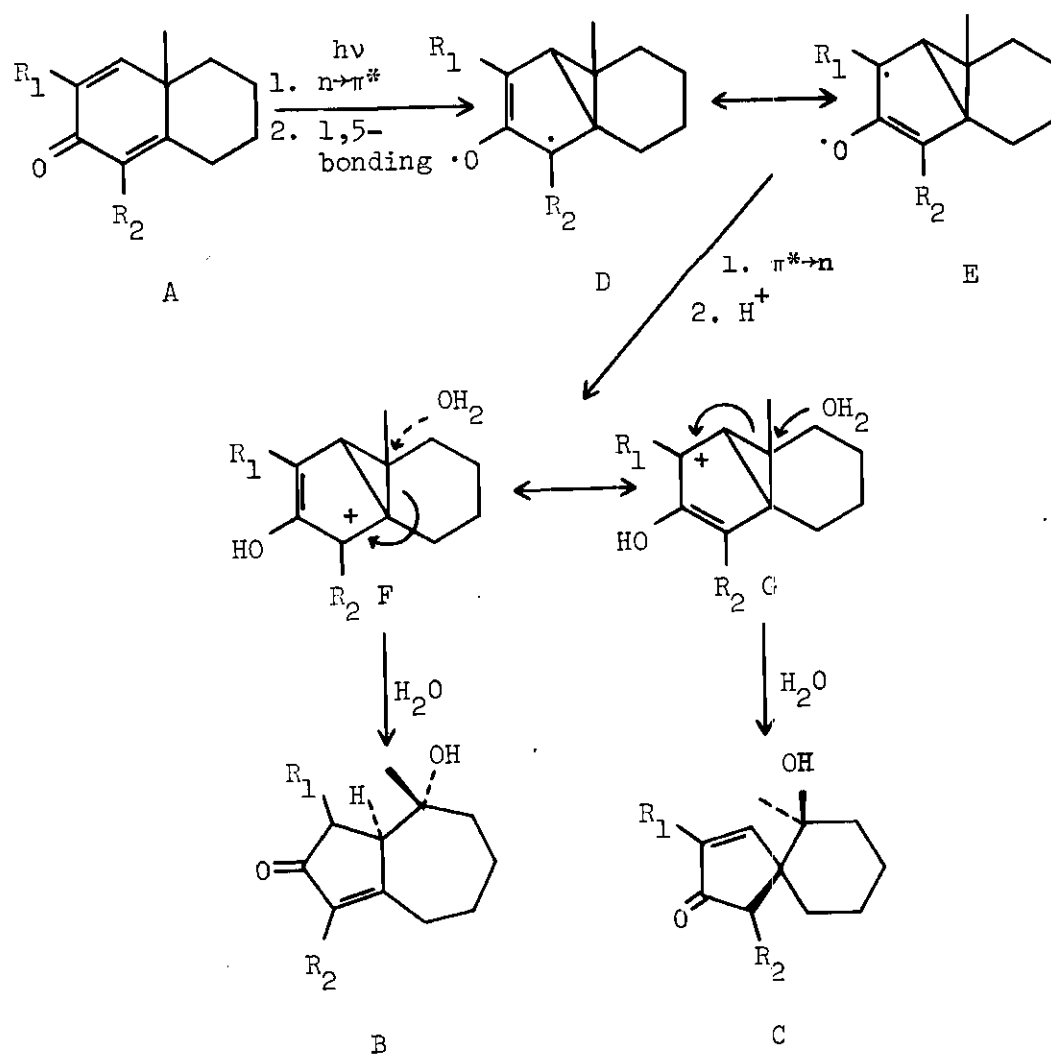
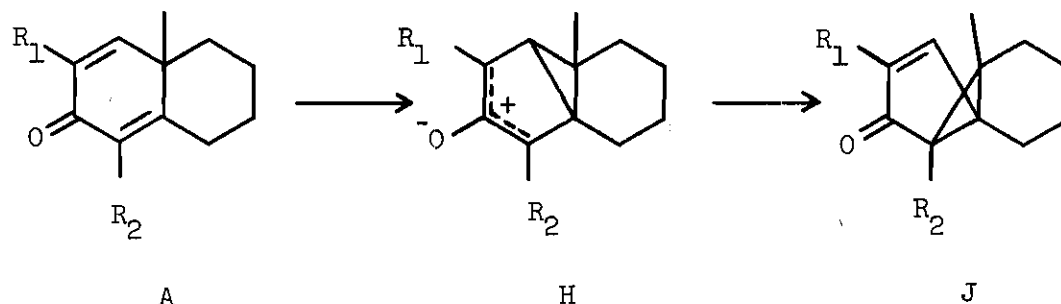


Chart II. Mechanism of Photochemical Rearrangements of Cross-Conjugated Cyclohexadienones.

In inert solvents the zwitterionic intermediate H, which is a precursor to the mesoionic species, normally undergoes a 1,4-sigmatropic rearrangement to give the lumiproduct J.



For the synthesis of cyclocolorenone it seemed desirable to use a dienone in which the necessary substituents were already present so that only one or two steps from the photoproduct would complete the synthesis. (-)-1,2-Dehydromaalienone (XI) (10,11), prepared in a straightforward manner from (-)-7-epi- $\alpha$ -cyperone (IX) (12,13), appeared to adequately satisfy this requirement. With the electron donating methyl group at C-4, irradiation in aqueous acetic acid would be expected to result in the formation of the hydroxy enone XII (11) which has the correct stereochemistry and substituents for conversion to cyclocolorenone.

However, during the course of our work Streith and Blind found that in acetic acid this dienone is stable to irradiation with ultraviolet light (11). They were still able to prepare the hydroxy enone XII by irradiation of 1,2-dehydro-epi- $\alpha$ -cyperone (XIV) followed by closure of the three-membered ring according to the procedure used by

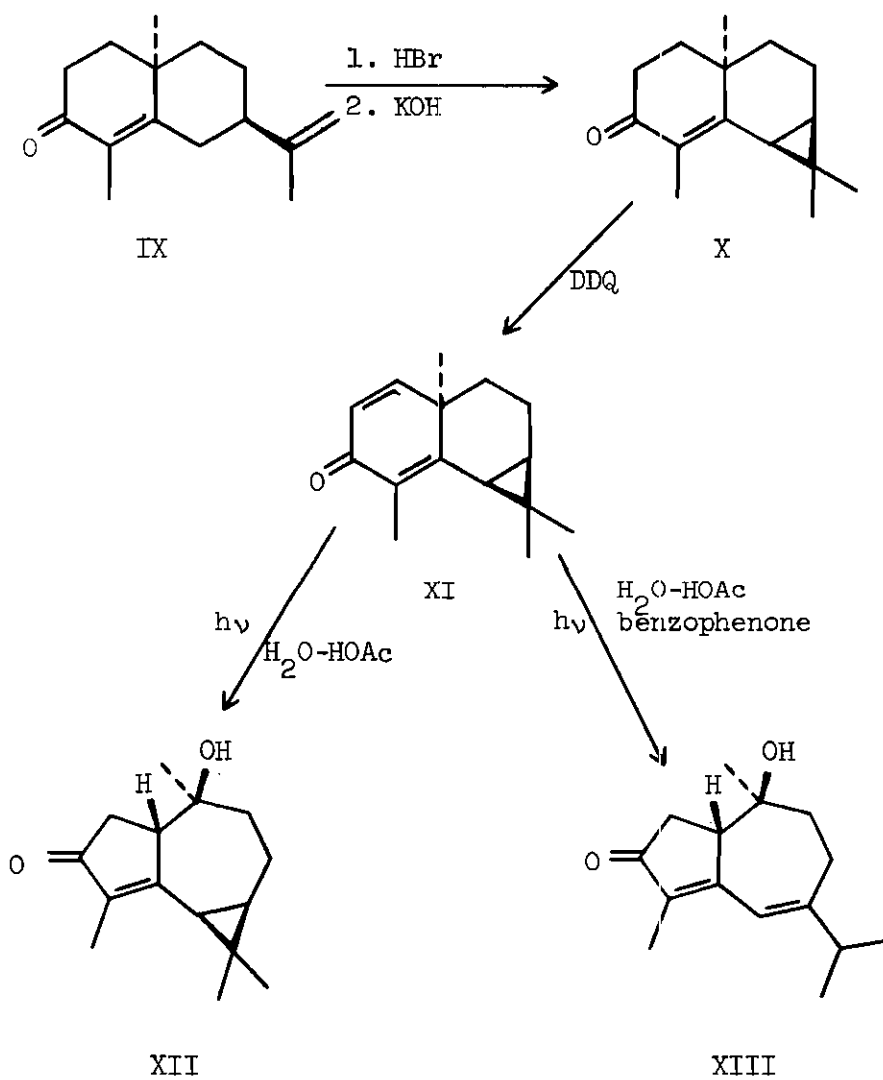
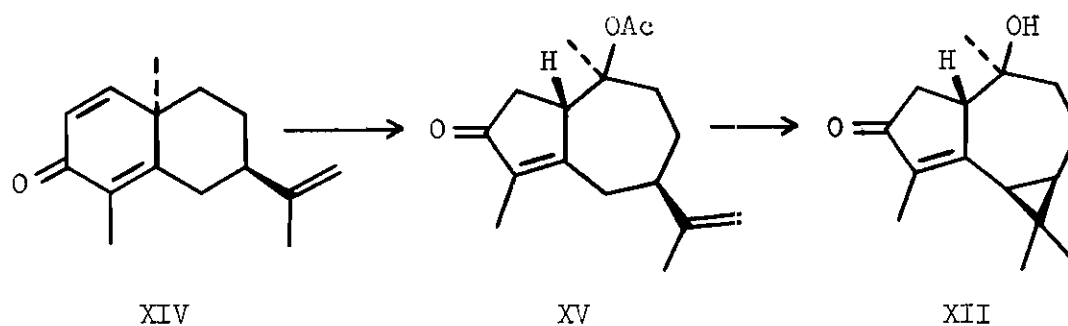
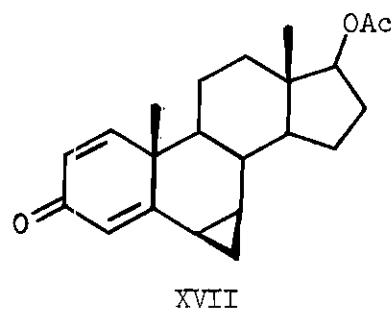
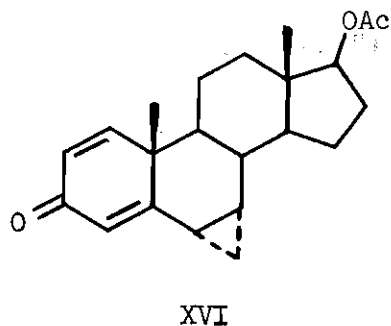


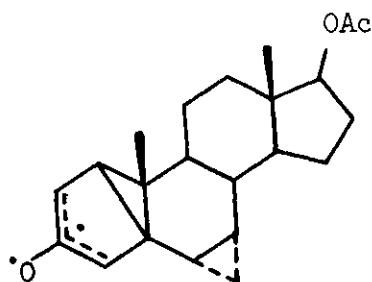
Chart III. Synthesis and Photolysis of Dehydromaalienone.

Büchi and coworkers in the epicyclocolorenone synthesis. Apparently epimerization at C-1 does not occur with the acetoxy ketone as it does with ketone VIII (see Chart I).



Kropp and Krauss also concluded that the dienone XI was photostable when it failed to rearrange on irradiation in ether or in benzene (10). An analogous compound, the steroidal dienone O-acetyl-1-dehydro-6 $\alpha$ ,7 $\alpha$ -methylene testosterone (XVI), was also found by Schaffner and coworkers to be unreactive toward ultraviolet light (14). On the other hand they found that the steroidal dienone XVII, in which the cyclopropyl ring and the 10-methyl group are cis oriented, is labile to ultraviolet light.

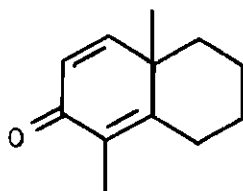




XVIII

Some theories have been advanced to explain the photostability of cyclopropyl dienones related to XI. One explanation is that a large amount of steric strain is introduced into the system when 1,5-bonding occurs to give two adjacent cis three-membered rings on the B ring (15). The primary photoproduct XVIII that does form would tend to give back starting material rather than forming the zwitterion and rearranging. This large steric strain does not occur in the primary photoproduct arising from XVII in which there is a trans arrangement of the cyclopropyl rings, so zwitterion formation and rearrangement can take place.

Kropp and Krauss have observed that there is no significant distortion of the cyclopropyl dienone system relative to the photolabile cyclopropyl enone and simple dienone systems X and XIX (10). They suggested that the observed difference in reactivity may be due to alteration of the electronic distribution in the excited state and that there may be a difference in whether the lowest excited state is  $n \rightarrow \pi^*$  or  $\pi \rightarrow \pi^*$ .



XIX

In the present work the photostability of XI was confirmed when after direct irradiation in aqueous acetic acid the starting material was recovered unchanged. Rearrangement was finally accomplished using benzophenone as a sensitizer in the irradiation, but the cyclopropyl ring was opened in the process to give the hydroxy dienone XIII (see Chart III) which could be of no further use in the synthesis.

So a new dienone had to be chosen which could be rearranged to a precursor of cyclocolorenone. Caine, DeBardleben, and Dawson have irradiated the 2-carboxydienone XX in a variety of solvents to give varying yields of XXI, XXII, XXIII, and XXIV (16). Decarboxylation of the  $\beta$ -keto acids initially produced in these rearrangements took place spontaneously. The electron withdrawing substituent at C-2 apparently stabilized the resonance structure of the mesoionic intermediate with the positive charge at C-4, and it was found that the rearrangement proceeded smoothly to give the 5/7-fused products and that the yields were higher than with the corresponding unsubstituted dienone (17). It was also noted that while unsubstituted and 4-methyl dienones require aqueous acidic media for rearrangement



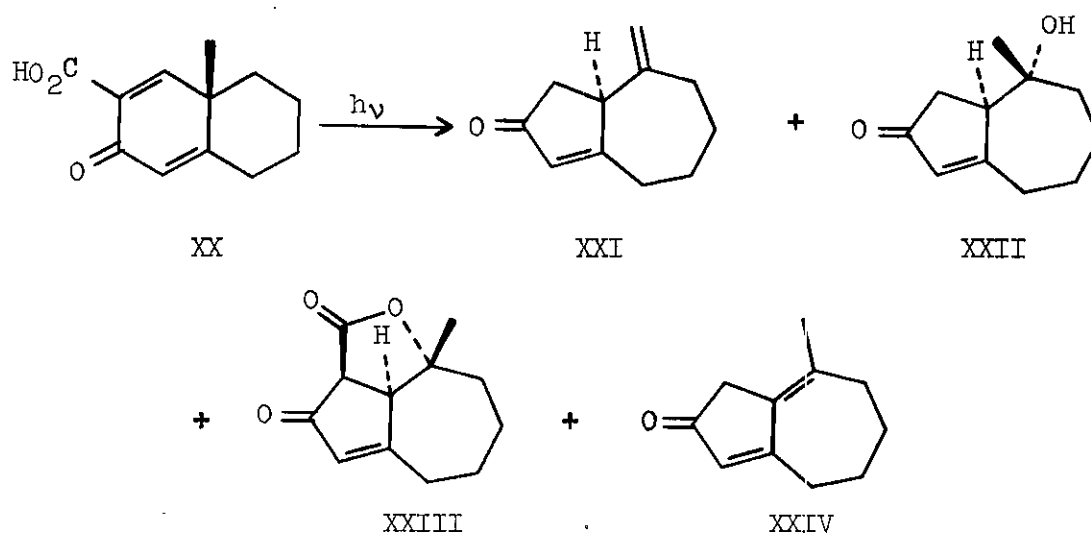


Chart IV. Photolysis of a 2-Carboxy Dienone.

to 5/7-fused products, the 2-carboxy dienone is easily converted in both nucleophilic and non-nucleophilic media.

So it was thought that a carboxy substituent at C-2 in XI might make the system more photolabile without causing the three-membered ring to open in the photolysis. 2-Carboxy-1,2-dehydro-maalienone (XXVII) was prepared from maalienone and irradiated in both aqueous acetic acid and anhydrous dioxane to give a hydroxy ketone XXVIII and the dienone XXIX, respectively. The dienone had the correct stereochemistry at all three asymmetric centers for conversion to (-)-cyclocolorenone. Examination of models of the photoproduct showed that the synthesis should be completed by catalytic hydrogenation of the exocyclic double bond which should take place from the  $\beta$  face of the molecule to produce the natural product with the

10 $\alpha$ -methyl group.

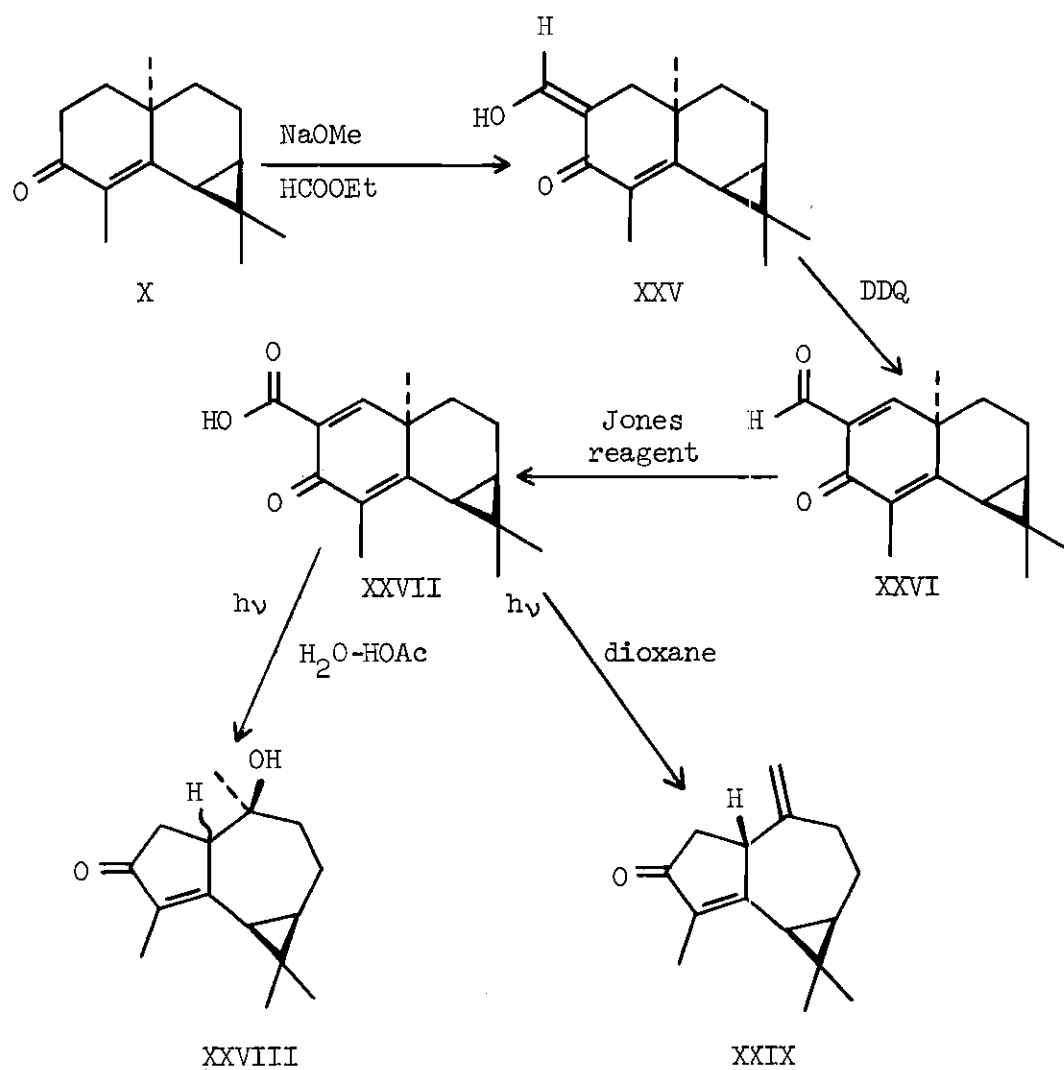


Chart V. Synthesis and Photolyses of 2-Carboxydehydromaalienone.

## CHAPTER II

## INSTRUMENTATION AND EQUIPMENT

When required for a reaction, a nitrogen atmosphere was established using an apparatus similar to that described by Johnson (18). Removal of solvents in vacuo was done using a Büchi Rotavapor rotary evaporator. A Hanovia 450-watt high pressure mercury lamp in a quartz or a Pyrex apparatus similar to that described by Kropp and Erman (17) was the light source for the irradiations. A slow stream of dried, prepurified nitrogen was bubbled through the solution for 10 minutes prior to and during all irradiations for deoxygenation and agitation of the solution. Hydrogenations were carried out in a Parr low pressure reaction apparatus. Column chromatographies were carried out using Grace grade 923, 100-200 mesh silica gel in the ratio of about 25 g silica gel per gram of mixture. Anhydrous magnesium sulfate was used as drying agent in reaction workups.

Infrared spectra were obtained using a Perkin-Elmer Model 137 or 457 recording spectrophotometer. For spectra run with a solvent, 0.1 mm sodium chloride cells were used. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or A-60D nuclear magnetic resonance spectrometer. Tetramethyl silane was used as an internal standard and the chemical shifts are reported in ppm downfield from it. The abbreviations s, d, t, q and m refer respectively to singlet, doublet, triplet, quartet and multiplet; coupling constants

(J) are given in Hz. Ultraviolet spectra were obtained using a Cary Model 14 or a Beckman Model DB-GT recording spectrophotometer using one centimeter balanced cells; 95 percent ethanol was the solvent. Mass spectral data were obtained on a Varian Associates Model M-66 medium resolution mass spectrometer with a 70 electron volt source. Gas chromatographic analyses were done using a Perkin-Elmer Model 881 flame ionization gas chromatograph using a 6 foot by 1/8 inch stainless steel column packed with 10 percent K-20M Carbowax on 60/80 Chromasorb W HMDS with a temperature program of 100° to 200°C at 12 degrees per minute, or a 6 foot by 1/8 inch stainless steel column packed with 10 percent SE-30 on 80/100 Chromasorb W HMDS with a temperature program of 100° to 225°C at 12 degrees per minute. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. Carbon and hydrogen analyses were performed by either Galbraith Laboratories, Knoxville, Tennessee, or Atlantic Microlab, Inc., Atlanta, Georgia.

## CHAPTER III

## EXPERIMENTAL

1,2-Dehydromaalienone (XI)

Maalienone (X) has been previously prepared by Büchi and coworkers (13). Compound XI was prepared using the general procedure of Burn, Kirk, and Petrow (19). A solution of 3.17 g (0.0145 mole) of X and 4.11 g (0.0181 mole) of 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) in 200 ml of dry benzene was placed in a 500 ml round-bottom flask equipped with a magnetic stirrer and reflux condenser and having a nitrogen atmosphere. To this was added 5 ml of glacial acetic acid, and the mixture was stirred at reflux for 43 hours, cooled to room temperature, and filtered to remove 2,3-dichloro-5,6-dicyano-p-hydroquinone (DDHQ). The solvent was removed in vacuo, and 200 ml of ether was added to the residue. The material which was insoluble in ether was discarded. The ether was removed in vacuo. Chromatography of the residue on 100 g of silica gel using hexane-ether as eluent afforded 0.4 g of the enone X (10 percent ether in hexane) and 0.74 g (27 percent) of the dienone XI (20 percent ether in hexane). The dienone crystallized on standing and was recrystallized from ethanol-water to give white crystals: mp 83°C; uv max (95 percent EtOH) 240 nm ( $\epsilon$  9,400) and 280 nm ( $\epsilon$  8,700); ir ( $\text{CHCl}_3$ ) 1656 ( $\alpha,\beta$ -unsaturated C=O), 1618 and 1603

(conjugated C=C), 1400, 1376 and 832  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  0.83 (s, 3H,  $\beta$ - $\text{CH}_3$  on cyclopropyl ring), 1.20 and 1.23 (2s, 6H,  $\alpha$ - $\text{CH}_3$  on cyclopropyl ring and 10- $\text{CH}_3$ ), 1.79 (d,  $J = 1$  Hz, 3H, 4- $\text{CH}_3$ ), and 6.02 and 6.62 (AB quartet,  $J_{AB} = 10$  Hz, 2H, 1,2-H).

Anal. Calculated for  $\text{C}_{15}\text{H}_{20}\text{O}$ : C, 83.33; H, 9.26.

Found: C, 83.10; H, 9.07.

#### Irradiation of 1,2-Dehydromaalienone (XI)

A solution of 0.3 g of XI in 250 ml of 45 percent aqueous acetic acid was irradiated with a 450-watt high pressure mercury lamp for one hour using a Pyrex probe. The solution was extracted well with 250 ml of ether, and the combined organic layers were washed with water to remove acetic acid. The ether solution was dried, and the solvent was removed to afford only the starting material.

A second irradiation was carried out for three hours under the same conditions except that a quartz probe was used. Workup of the photolysis mixture as before yielded only the starting material and some intractible polymeric material. Also, only the starting material was recovered when XI was irradiated for a 30 hour period using a quartz probe.

#### Irradiation of 1,2-Dehydromaalienone (XI)

##### in the Presence of Benzophenone

A solution of 1.92 g (0.0105 mole) of benzophenone and 0.78 g (0.00361 mole) of XI in 300 ml of 55 percent aqueous acetic acid was irradiated with a 450-watt high pressure mercury lamp for five hours

using a quartz probe. The solution was extracted well with 300 ml of ether, and the ether solution was washed with water to remove acetic acid. The ether solution was dried, and the solvent was removed in vacuo to yield 2.65 g of a yellow oil which was chromatographed on 60 g of silica gel. Elution with 10 percent ether in hexane afforded benzophenone and with 20 percent ether in hexane yielded 0.175 g of the starting material. Further elution with ether gave 0.259 g (0.001111 mole) (40 percent) of the hydroxy dienone XIII which crystallized on standing: mp 124-6°C; uv max (95 percent EtOH) 296 nm; ir ( $\text{CHCl}_3$ ) 3400 (OH), 1680 ( $\alpha,\beta$ -unsaturated C=O), 1625 (conjugated C=C), 1460, 1382, 1345 and 1090  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.99 (s, 3H, 10- $\text{CH}_3$ ), 1.09 (d,  $J = 7$  Hz, 6H, isopropyl  $\text{CH}_3$ 's), 1.73 (d,  $J = 1.5$  Hz, 3H, 4- $\text{CH}_3$ ), 3.40 (broad absorption, 2H, 2- $\text{CH}_2$ ), 6.32 (s, 1H, 6-H); mass spectrum (70eV)  $m/e$  234 ( $\text{M}^+$ ), 219 ( $\text{M}^+ - \text{CH}_3$ ), 216 ( $\text{M}^+ - \text{H}_2\text{O}$ ), and 191 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ), EMD 234.164 (Calculated: 234.162).

#### 1,2-Dehydro- $\beta$ -cyperone (XXXV)

$\beta$ -Cyperone (XXXIII) was prepared by the procedure of Howe and McQuillin (12). Compound XXXV was prepared by the general procedure of Burn, Kirk, and Petrow (19). A solution of 3.17 g (0.0145 mole) of XXXIII and 4.11 g (0.0181 mole) of DDQ in 200 ml of dry benzene was placed in a 500 ml round-bottom flask equipped with a magnetic stirrer and reflux condenser and having a nitrogen atmosphere. To this was added 5 ml of glacial acetic acid, the mixture was stirred at reflux for 40 hours, cooled to room temperature, and

filtered to remove DDHQ. The solvent was removed in vacuo, and 150 ml each of ether and water were added to the residue. The layers were separated, and the aqueous layer was extracted several times with 30 ml portions of ether. The combined organic layers were then washed several times with water, dried, and the solvent was removed in vacuo. Chromatography of the residue on 100 g of silica gel using hexane-ether as eluent afforded 0.3 g of the dienone XXXIII (10 percent ether in hexane) and 0.57 g (20 percent) of the trienone XXXV (15 percent ether in hexane): uv max (95 percent EtOH) 236 nm and 313 nm; ir ( $\text{CHCl}_3$ ) 1650 ( $\alpha,\beta$ -unsaturated C=O), 1603 (conjugated C=C), 1460, 1404, 1329, 1090 and 832  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  1.12 (d,  $J = 6.5$  Hz, 6H, isopropyl  $\text{CH}_3$ 's), 1.14 (s, 3H, 10- $\text{CH}_3$ ), 1.89 (s, 3H, 4- $\text{CH}_3$ ), 6.41 (s, 1H, 6-H), and 6.14 and 6.78 (AB quartet,  $J_{AB} = 10$  Hz, 2H, 1,2-H); mass spectrum (70 eV)  $m/e$  216 ( $\text{M}^+$ ), 201 ( $\text{M}^+ - \text{CH}_3$ ), and 173 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ), EMD 216.151 (calculated: 216.151).

#### Irradiation of 1,2-Dehydro- $\beta$ -cyperone (XXXV)

A solution of 0.7 g (0.00324 mole) of XXXV and 1.73 g (0.0095 mole) of benzophenone in 300 ml of 55 percent aqueous acetic acid was irradiated with a 450-watt high pressure mercury lamp for five hours using a Pyrex probe. The solution was extracted well with 300 ml of ether, and the ether solution was washed free of acetic acid. The ether solution was dried, and the solvent was removed in vacuo. Chromatography of the residue on silica gel with hexane-ether and methanol afforded 0.22 g (29 percent) of the hydroxy dienone XIII (ether and methanol) which crystallized on standing: mp 125°C; uv, ir



and nmr identical to those of the product of the dehydromaalienone-benzophenone photolysis.

2-Hydroxymethylenemaalienone (XXV)

Compound XXV was prepared by a procedure similar to that employed by Edwards and coworkers (20). A suspension of 1.86 g (0.0775 mole) of sodium hydride in 100 ml of dry benzene was stirred in a 500 ml round-bottom flask equipped with a reflux condenser and dropping funnel and having a nitrogen atmosphere. To this suspension was added 1.67 g (0.0522 mole) of dry methanol, the mixture was heated to boiling, cooled to room temperature, and 5.735 g (0.0775 mole) of ethyl formate (freshly distilled from  $P_2O_5$ ) was added in a thin stream. The mixture was stirred 30 minutes and cooled in an ice bath, and 6.75 g (0.0310 mole) of X in 100 ml of dry benzene was added dropwise with cooling. When the addition was complete, the ice bath was removed, and the mixture was stirred at room temperature overnight. The mixture was acidified with 100 ml of cold 5 percent sulfuric acid and stirred five minutes. The layers were separated, and the aqueous layer was extracted three times with 30 ml portions of 50 percent benzene-ether. The combined organic layers were extracted with 250 ml of cold 2 percent potassium hydroxide. The basic extracts were washed once with ether and then acidified with dilute hydrochloric acid. The aqueous mixture was then extracted several times with 30 ml portions of 50 percent benzene-ether, and the combined organic layers were washed once with brine and dried over magnesium sulfate.

Removal of the solvent in vacuo gave 7.0 g (92 percent) of XXV as a yellow oil: uv max (95 percent EtOH) 288 nm and 312 nm; ir (film) 1638 ( $\alpha,\beta$ -unsaturated C=O), 1612, 1570, 1414, 1379, 1352, 1337, 1220, 1060 and 896  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.96 and 1.04 (2s, 6H,  $\beta\text{-CH}_3$  on cyclopropyl ring and 10- $\text{CH}_3$ ), 1.20 and 1.15 (2s, 3H,  $\alpha\text{-CH}_3$  on cyclopropyl ring), 1.80 and 1.88 (2d,  $J = 1$  Hz, 3H, 4- $\text{CH}_3$ ), 6.31 and 7.40 (2s, 1H, 2-CH), and 13.91 (broad s, 1H, OH); mass spectrum (70 eV)  $m/e$  246 ( $\text{M}^+$ ), 231 ( $\text{M}^+ - \text{CH}_3$ ), and 203 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ), EMD 246.203 (calculated: 246.162).

2-Formyl-1,2-dehydromaaalienone (XXVI)

The oxidation of the hydroxymethylene derivative XXV was carried out according to the procedure of Edwards and coworkers (20). A solution of 1.5 g (0.0061 mole) of XXV in 60 ml of dioxane (freshly distilled from sodium hydroxide and sodium) was treated with a solution of 1.53 g (0.00674 mole) of DDQ in 60 ml of dioxane in a 1000 ml Erlenmeyer flask. The reaction mixture was swirled at room temperature for three minutes and then was diluted with 500 ml of benzene. During the reaction DDHQ was formed and precipitated from the solution. The mixture was filtered through a short acid alumina column, and the alumina was washed with 700 ml of benzene. The solvents were removed in vacuo to give 2.65 g of crude product. Chromatography on 60 g of silica gel using hexane-ether as eluent afforded 0.987 g (66 percent) of the formyl compound XXVI as a yellow oil (10 percent ether in hexane): uv max (95 percent EtOH) 230 nm and 286 nm; ir (film) 1703 ( $\alpha,\beta$ -unsaturated C=O), 1651 ( $\alpha,\beta$ -unsaturated C=O), 1605 (conjugated C=C), 1462, 1412, 1378, 1361,

1271, 1125 and  $834\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.83 (s, 3H,  $\beta\text{-CH}_3$  on cyclopropyl ring), 1.23 (s, 3H,  $\alpha\text{-CH}_3$  on cyclopropyl ring), 1.33 (s, 3H, 10- $\text{CH}_3$ ), 1.92 (d,  $J = 1\text{ Hz}$ , 3H, 4- $\text{CH}_3$ ), 7.48 (s, 1H, 1-H), and 10.22 (s, 1H, CHO).

2-Carboxy-1,2-dehydromaalienone (XXVII)

The oxidation of the formyl compound XXVI was accomplished using Jones reagent (21). A mixture of 7.5 g (0.075 mole) of chromium trioxide in 6 ml of sulfuric acid was added to 13.5 ml of water and cooled to  $0^\circ\text{C}$ . A solution of 2.96 g (0.0121 mole) of XXVI in 120 ml of acetone was also cooled to  $0^\circ\text{C}$ , and 10 ml of Jones reagent was added to it dropwise over 20 minutes with stirring and cooling. The solution was stirred five minutes after addition was complete, and 400 ml of brine was added. The mixture was extracted several times with 40 ml portions of ether, the combined organic layers were washed once with brine and then extracted with 150 ml of dilute sodium bicarbonate. The basic extracts were washed once with 30 ml of ether, acidified with dilute sulfuric acid, and extracted well with 100 ml of ether. The extracts were washed with brine until neutral and dried, and the ether was removed in vacuo to leave 0.96 g (30 percent) of crystalline XXVII. Recrystallization from ether gave an analytical sample: mp  $100\text{--}2^\circ\text{C}$ ;  $[\alpha]_D - 48^\circ$  ( $\text{CHCl}_3$ ); uv max (95 percent EtOH) 220 nm ( $\epsilon$  10,300) and 297 nm ( $\epsilon$  4,500); ir ( $\text{CHCl}_3$ ) 2725 (OH), 1732 (carboxyl C=O), 1644 ( $\alpha,\beta$ -unsaturated C=O), 1580 (C=C), 1444, 1402, 1280, 1060 and  $910\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.84 (s, 3H,  $\beta\text{-CH}_3$  on cyclopropyl ring), 1.27 (s, 3H,  $\alpha\text{-CH}_3$  on cyclopropyl ring), 1.38 (s, 3H, 10- $\text{CH}_3$ ), 1.97 (d,  $J = 1\text{ Hz}$ , 3H, 4- $\text{CH}_3$ ), 8.16 (s, 1H, 1-H),

and 11.84 (broad s, 1H, COOH); mass spectrum (70 eV) m/e 260 ( $M^+$ ), 245 ( $M^+ - CH_3$ ), 242 ( $M^+ - H_2O$ ), and 227 ( $M^+ - CH_3, H_2O$ ), EMD 260.130 (calculated: 260.141).

Anal. Calculated for  $C_{16}H_{20}O_3$ : C, 73.85; H, 7.69. Found: C, 73.61; H, 7.64.

In an alternate method of isolation and purification, brine was added to the reaction mixture, and the mixture was extracted well with 200 ml of ether. The combined organic layers were then washed with brine until neutral and dried, and the solvent was removed in vacuo to leave about 1.5 g of a yellow oil. Chromatography on 30 g of silica gel using hexane-ether as eluent afforded 0.75 g (24 percent) of the 2-carboxydienone XXVII (30 percent ether in hexane).

#### Irradiation of 2-Carboxy-1,2-dehydromaaalienone (XXVII)

A solution of 0.60 g (0.00231 mole) of XXVII in 300 ml of 45 percent aqueous acetic acid was irradiated with a 450-watt high pressure mercury lamp for two hours using a Pyrex probe. The reaction mixture was frozen, and the solvents were removed by lyophilization to leave 0.482 g of an oil which was chromatographed on 15 g of silica gel. Elution with 50 percent ether in hexane afforded 0.02 g of the starting material and with 75 percent ether in hexane yielded 0.137 g (26 percent) of the hydroxy enone XXVIII: uv max (95 percent EtOH) 241 nm; ir (film) 3400 (OH), 1686 ( $\alpha,\beta$ -unsaturated C=O), 1630 (conjugated C=C), 1460, 1383, 1337, 1120, 1091 and 735  $cm^{-1}$ ; nmr ( $CDCl_3$ )  $\delta$  0.89 (s, 3H,  $\beta$ - $CH_3$  on cyclopropyl ring), 0.97 (s, 3H,  $\alpha$ - $CH_3$  on cyclopropyl

ring), 1.09 (s, 3H, 10-CH<sub>3</sub>), and 1.72 (d, J = 1 Hz, 3H, 4-CH<sub>3</sub>); mass spectrum (70 eV) m/e 234 (M<sup>+</sup>), 216 (M<sup>+</sup>-H<sub>2</sub>O), and 191 (M<sup>+</sup>-CH(CH<sub>3</sub>)<sub>2</sub>), EMD 234.164 (calculated: 234.162).

Attempted Dehydration of 10-Hydroxycyclocolorenone (XXVIII)

A solution of 0.060 g (0.00026 mole) of XXVIII in 2 ml of dry pyridine was placed in a 10 ml round-bottom flask equipped with a magnetic stirrer and having a nitrogen atmosphere and was cooled to 0°C. To this solution was added 0.25 ml of thionyl chloride dropwise with stirring and cooling. The solution was stirred at 0°C for 30 minutes, and 3 ml of water was added dropwise with cooling. The mixture was extracted well with 10 ml of ether, and the combined organic layers were washed with brine and dried. Removal of the solvent in vacuo afforded 0.0425 g of a dark brown oil. Examination of the oil by spectroscopic methods showed that it contained no material having properties consistent with those of the expected dienone.

In an alternate procedure, 0.060 g (0.00026 mole) of XXVIII was dissolved in 1 ml of dry acetonitrile and added to a solution of 0.3 g (0.00126 mole) of carboxysulfamoyl triethyl ammonium hydroxide inner salt, methyl ester (22) in 2 ml of dry acetonitrile in a 10 ml round-bottom flask maintained under a nitrogen atmosphere. The solution was stirred at 45°C for 1.5 hours and cooled, and 2 ml of water was added. The mixture was extracted with ether, and the extracts were washed with water, dried, and concentrated to give

0.0449 g of a dark brown oil which could not be identified by nmr or ir analysis.

Irradiation of 2-Carboxy-1,2-dehydromaaalienone

(XXVII) in Dioxane

A solution of 0.65 g (0.0025 mole) of XXVII in 300 ml of dry dioxane was irradiated with a 450-watt high pressure mercury lamp for five hours using a Pyrex probe. All of the solvent was removed in vacuo to leave 0.60 g of an oil which appeared to be 80 percent dienone XXIX by nmr and glc (Carbowax column) analyses. Chromatography of the oil on silica gel using hexane-ether as eluent afforded 0.19 g (40 percent) of XXIX (20 percent ether in hexane) and 0.08 g of the starting material (20 percent ether in hexane). The product crystallized to give an analytical sample: mp  $57^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}} -417^{\circ}$  ( $\text{CHCl}_3$ ); uv max (95 percent EtOH) 262 nm ( $\epsilon$  7,500); ir ( $\text{CHCl}_3$ ) 1695 ( $\alpha,\beta$ -unsaturated  $\text{C}=\text{O}$ ), 1630 (conjugated  $\text{C}=\text{C}$ ), 1385, 1336, 1308 and  $885\text{ cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  1.00 (s, 3H,  $\beta$ - $\text{CH}_3$  on cyclopropyl ring), 1.26 (s, 3H,  $\alpha$ - $\text{CH}_3$  on cyclopropyl ring), 1.70 (d,  $J = 2\text{ Hz}$ , 3H, 4- $\text{CH}_3$ ), 3.40 (broad absorption,  $w_{\text{H}} = 10\text{ Hz}$ , 1H, 1-H), 4.84 (s, 1H,  $\text{C}=\text{CH}_2$ ), and 4.96 (t,  $J = 1.5\text{ Hz}$ , 1H,  $\text{C}=\text{CH}_2$ ); mass spectrum (70 eV)  $m/e$  216 ( $\text{M}^+$ ), 201 ( $\text{M}^+ - \text{CH}_3$ ), and 173 ( $\text{M}^+ - \text{CH}(\text{CH}_3)_2$ ), EMD 216.132 (calculated: 216.151).

Anal. Calculated for  $\text{C}_{15}\text{H}_{20}\text{O}$ : C, 83.33; H, 9.26. Found: C, 83.26; H, 9.26.

(-)-Cyclocolorenone (I)

A solution of 0.060 g (0.000278 mole) of XXIX in 20 ml of

ethyl acetate was shaken with 0.015 g of palladium on carbon catalyst in a Parr hydrogenation apparatus under 20 pounds of hydrogen for 40 minutes. The mixture was filtered to remove the catalyst, and the solvent was removed in vacuo to give 0.060 g of an oil which was shown to be greater than 85 percent one component by nmr and glc (Carbowax column) analyses. Distillation of the product afforded 0.024 g (40 percent) of (-)-cyclocolorenone (I) as a colorless oil: bp 113°C (bath temperature) (0.05 mm);  $[\alpha]_D^{25} -44.0^\circ$  (CHCl<sub>3</sub>); uv max (95 percent EtOH) 261 nm; ir (CHCl<sub>3</sub>) 1692 ( $\alpha,\beta$ -unsaturated C=O), 1625 (conjugated C=C), 1460, 1414, 1387, 1339, 1310, 1120, 1068 and 840 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>)  $\delta$  0.81 (d, J = 6.5 Hz, 3H, 10-CH<sub>3</sub>), 1.03 (s, 3H,  $\beta$ -CH<sub>3</sub> on cyclopropyl ring), 1.25 (s, 3H,  $\alpha$ -CH<sub>3</sub> on cyclopropyl ring), 1.66 (d, J = 2 Hz, 3H, 4-CH<sub>3</sub>), and 2.93 (broad absorption,  $w_h = 12$  Hz, 1H, 1-H):

In an alternate procedure, 0.060 g of XXIX, 0.060 g of the homogeneous catalyst tris(triphenylphosphine)chlororhodium(I) (23), and 20 ml of benzene were shaken in a Parr apparatus under 30 pounds of hydrogen for 30 hours. The solution was filtered through 20 g of silica gel, the silica gel was washed with 30 ml of ether, and the solvents were removed. Ether (20 ml) was added to the residue, and the material insoluble in ether was removed by filtration. Evaporation of the solvent left 0.057 g of an oil which was distilled to give 0.021 g of a yellow oil: bp 104°C (bath temperature) (0.05 mm). Nmr and glc analyses showed the oil to be a 70:30 mixture of (-)-cyclo-

colorenone and its C-10 epimer XLI. Although this mixture was not further purified, it was observed that the 10-CH<sub>3</sub> doublet for XLI was at lower field (0.88 ppm) than that for cyclocolorenone. There were no other noticeable differences in the nmr or ir spectra, but the uv spectrum showed an slightly lower  $\lambda_{\text{max}}$  (257 nm) than pure cyclocolorenone.



## CHAPTER IV

## DISCUSSION OF RESULTS

As stated in the first chapter, the principal goal of this research was to complete a synthesis of the naturally occurring sesquiterpene ketone (-)-cyclocolorenone. In accomplishing this goal a good deal of interesting and useful information was gained on various aspects of the synthesis including the photochemistry of 6/6-fused cross-conjugated cyclohexadienones with a cyclopropyl ring fused to the B ring of the molecule.

The starting enone in this synthesis was prepared by the standard method of condensing a vinyl ketone with a cyclohexanone derivative. (+)-Dihydrocarvone was first prepared by the reduction of the endocyclic double bond of (-)-carvone with zinc and sodium hydroxide (24). Then following the procedure of Marshall for the preparation of (-)-7-epi- $\alpha$ -cyperone (IX), a base catalyzed condensation of ethyl vinyl ketone and (+)-dihydrocarvone was carried out at 0°C (25). The  $\beta$  isopropenyl group in the dihydrocarvone would lead to the desired  $\beta$  cis-fused cyclopropyl ring after the ring closure discussed below. Workup without acidification of the reaction mixture resulted in a 70:30 mixture of ketols XXX and XXXI. Crystallization of XXX from the mixture allowed easy separation of the isomers. This ketol, with the required  $\alpha$  angular methyl group, was then dehydrated by refluxing in ethanolic potassium hydroxide to give IX

with the correct stereochemistry at both asymmetric carbons. It was found that acidification of the reaction mixture during the workup procedure caused dehydration of the ketol products to enones, thus making an easy separation of the isomers impossible.

Treatment of IX with hydrogen bromide in acetic acid at 15°C after the procedure of Büchi (13) gave the tertiary bromide XXXII which was not isolated. The crude product was dehydrohalogenated on refluxing with methanolic potassium hydroxide. Workup gave about 60 percent of the desired maalienone (X) and about 30 percent of  $\beta$ -cyperone (XXXIII), and these products were separated by distillation.  $\beta$ -cyperone was possibly produced in the hydrogen bromide-acetic acid solution by acid catalyzed isomerization of the double bond into the B ring. This reaction is known to occur under different acidic conditions and will be mentioned later. A ring is normally formed instead of a double bond on dehydrohalogenation of XXXII due to the increased lability of the C-6 hydrogen in the enolizable position allylic to the  $\alpha,\beta$ -unsaturated carbonyl. It is possible, however, that dehydrohalogenation in the methanolic alkali gave a side-chain double bond which was then isomerized into the B ring producing  $\beta$ -cyperone.

Finally preparation of the desired dienone XI was completed by oxidation of maalienone using a modification of the procedure of Burn, Kirk, and Petrow (19). Treatment with 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) in refluxing benzene in the presence of a small amount of acetic acid provided a 27 percent yield of the product which is reasonable for this type of oxidation reaction. The crystalline

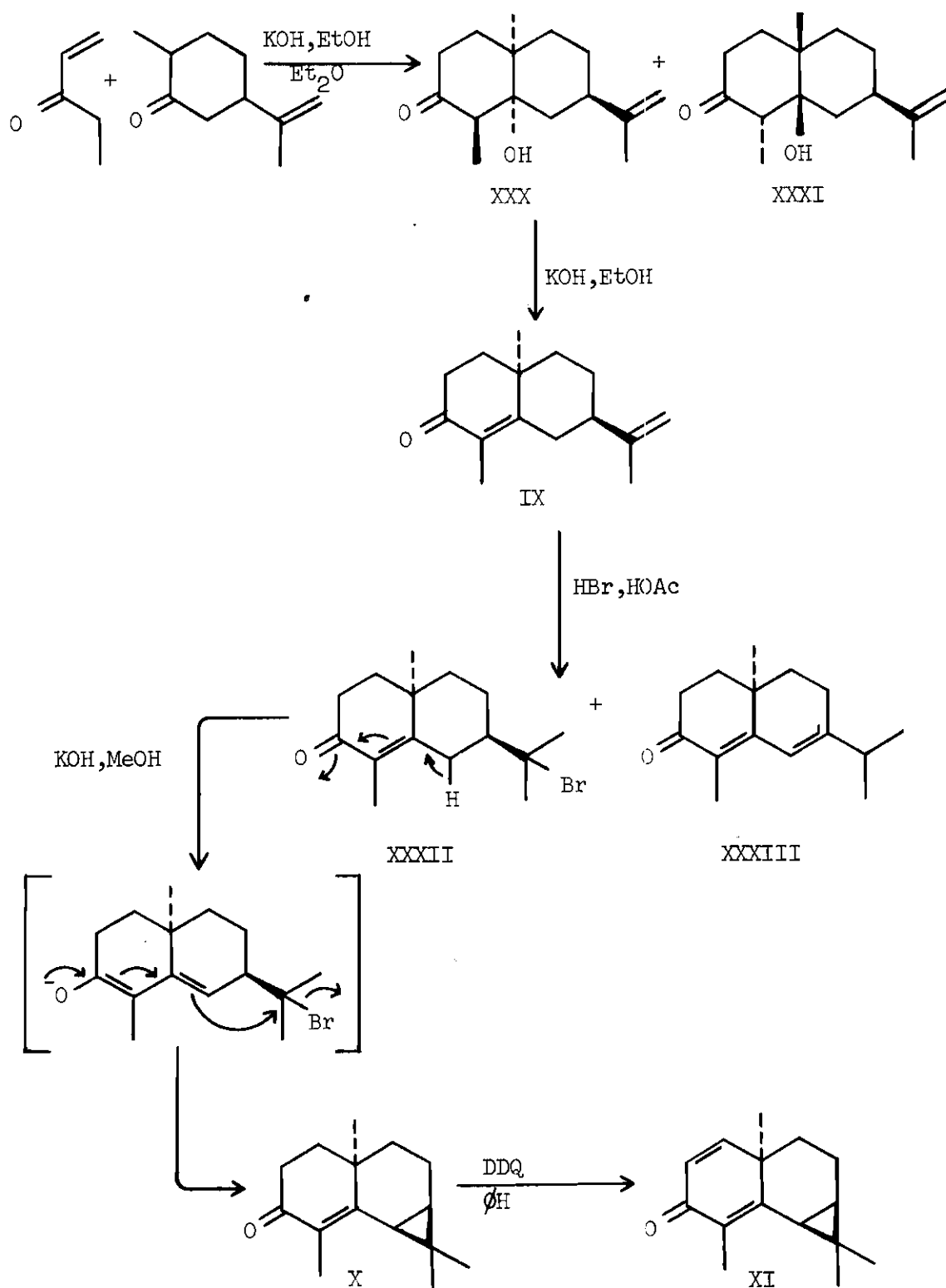
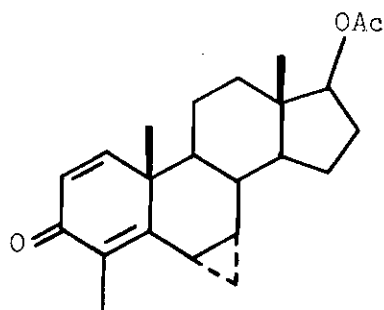


Chart VI. Synthesis of Dehydromaaalienone.

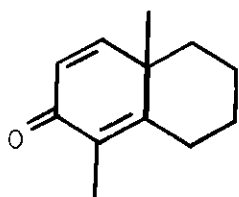
product melted at  $83^{\circ}\text{C}$  and gave spectra identical to those given by authentic samples (10,11).

Dehydromaaalienone had the correct substituents and stereochemistry for the photochemical conversion into a precursor of (-)-cyclocolorenone (see Chapter I). However irradiation in aqueous acetic acid under a variety of conditions did not produce the expected rearrangement to the hydroxy enone XII. Irradiations for periods of from 1 to 30 hours in both Pyrex and quartz apparatus gave the starting dienone as the only identifiable compound isolated. Streith and Blind have also found the dienone to be photostable (11), and Kropp and Krauss obtained the same results on irradiation of the dienone in the inert solvents benzene and ether (10). The steroidal dienone, O-acetyl-1-dehydro- $6\alpha,7\alpha$ -methylene testosterone (XVI), related to XI has also been shown to be stable toward ultraviolet irradiation (14).

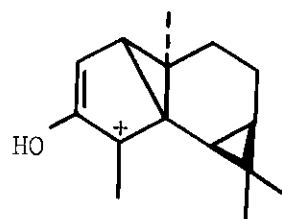
So it appeared that the cyclopropyl ring fused to the B ring of dienones inhibits the rearrangement normally observed with 4-methyl dienones of type XIX. The three-membered ring, with its tendency to extend the conjugation of the  $\alpha,\beta$ -unsaturated system (see Chapter I), may influence the energy and electronic distribution of the excited state species so that the excited state either is not reached under the normal conditions of the irradiation or cannot form the proposed cyclopropyl intermediate XXXIV. Also, strain arising from the presence of two adjacent three-membered rings may not allow the formation of XXXIV (10,15).



XVI



XIX



XXXIV

In trying to determine whether or not the excited state was reached, another attempt to achieve the desired  $n \rightarrow \pi^*$  electronic transition was made using benzophenone as a sensitizer. Benzophenone is readily raised to the singlet excited state on irradiation with ultraviolet light. The singlet in turn gives the triplet excited state, and energy may then be transferred to give the triplet of another species more easily than by direct irradiation (26). Irradiation in the presence of benzophenone did indeed lead to rearrangement of XI to give one major product in about 30 percent yield. However, the product was the ring-opened hydroxy dienone XIII as evidenced by the presence of an absorption at 6.32 ppm in the nmr spectrum for a vinyl proton on a conjugated double bond. Other spectral properties which point to the hydroxy dienone structure are the uv maximum at 296 nm characteristic of linearly conjugated dienones, ir absorptions at 3400, 1680, and 1625  $\text{cm}^{-1}$  indicating hydroxyl and  $\alpha, \beta$ -unsaturated carbonyl groups, and mass spectrum peaks at 234 ( $M^+$ ) and 216 ( $M^+ - \text{H}_2\text{O}$ ). Since there was no means by which the cyclopropyl ring could be reclosed, this compound was of no further

use in the synthetic work.

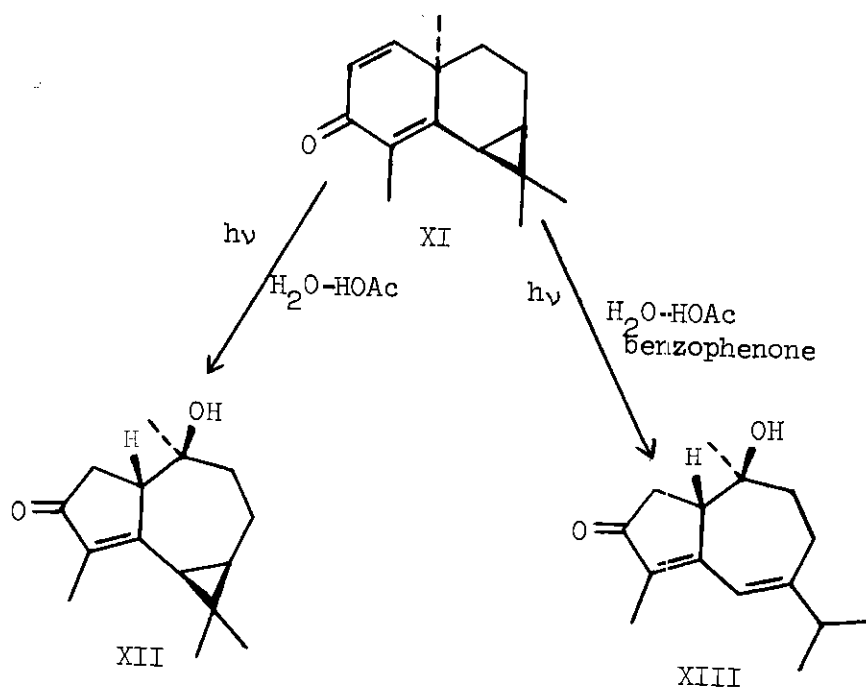


Chart VII. Photolysis of Dehydromaaalienone.

In considering possible ways to avoid the problem of cyclopropyl ring opening, it seemed desirable to determine the stage in the rearrangement at which the ring opening reaction occurred. The possibility that the trienone XXXV was an intermediate in the reaction was demonstrated as follows. (-)-Epi- $\alpha$ -cyperone (IX) was first converted in quantitative yield into  $\beta$ -cyperone (XXXIII) by treatment with cold 50 percent sulfuric acid following the procedure of Howe and McQuillin (12). The latter was then oxidized to the trienone XXXV with DDQ in benzene. The yield was approximately the

same as that obtained in the oxidation of (-)-maalienone. The trienone was then photolyzed in the presence of benzophenone, and the hydroxy ketone XIII was isolated in 30 percent yield from this irradiation. No other photoproducts were isolated.

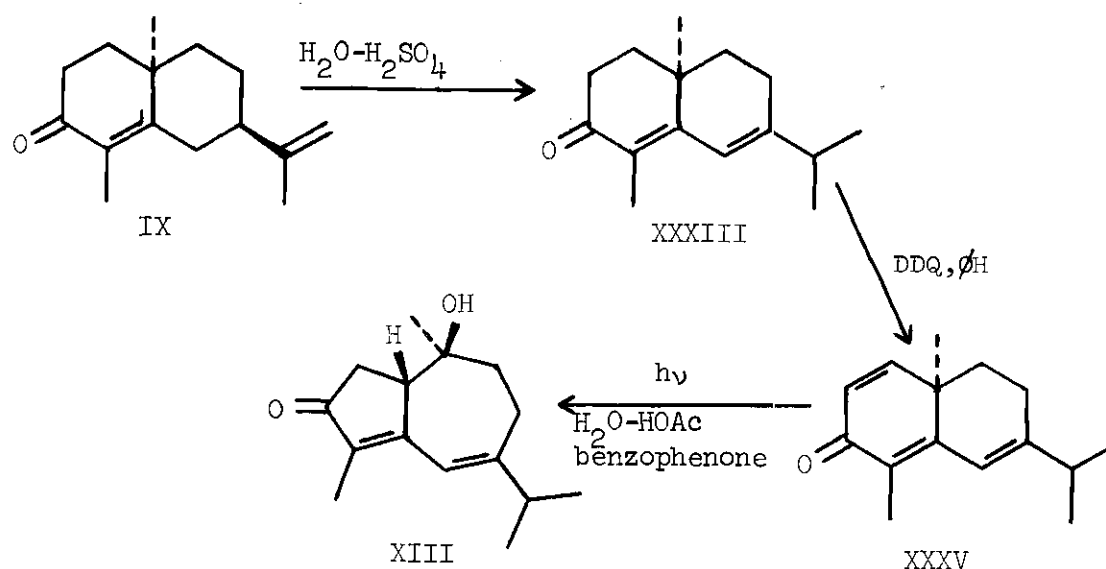


Chart VIII. Synthesis and Photolysis of Dehydro- $\beta$ -cyperone.

This rearrangement showed that it is possible that the trienone XXXV is an intermediate in the rearrangement of XI. Kropp has studied the photochemical opening of the cyclopropyl ring of the enone X to give  $\beta$ -cyperone and has proposed that the opening proceeds by way of the zwitterionic intermediate XXXVI (10). So it seems reasonable to assume that the photochemical rearrangement of XI proceeds by the analogous route through XXXVII.

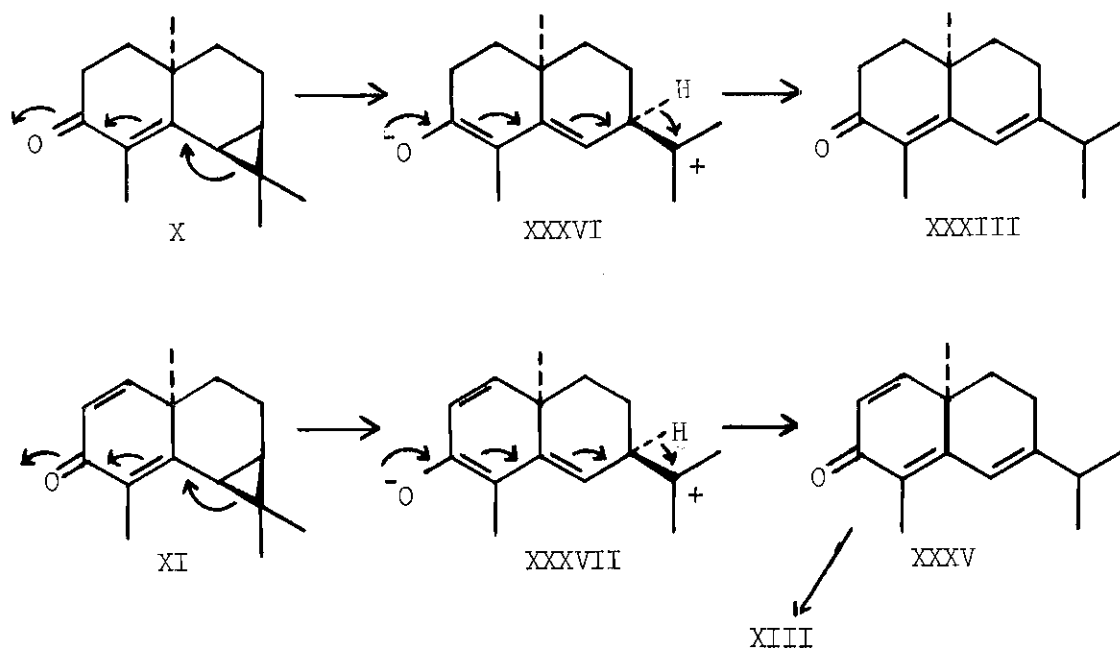


Chart IX. Rearrangements of Tricyclic Enone and Dienone.

Since the photochemical conversion of XI into a precursor of cyclocolorone did not appear to be possible, another route to the natural product had to be developed. As was discussed in Chapter I, Caine, DeBardeleben, and Dawson found that various 5/7-fused products were formed in the rearrangements of the 2-carboxy dienone XX (16). In aqueous acetic acid and aqueous dioxane the major product was the hydroxy enone XXII. With anhydrous dioxane as the solvent the dienone XXI was the major product. The proposed routes of the rearrangements were through the zwitterionic intermediate XXXVIII and either  $\beta$ -keto acid XXXIX or XL which would readily decarboxylate to yield the products.



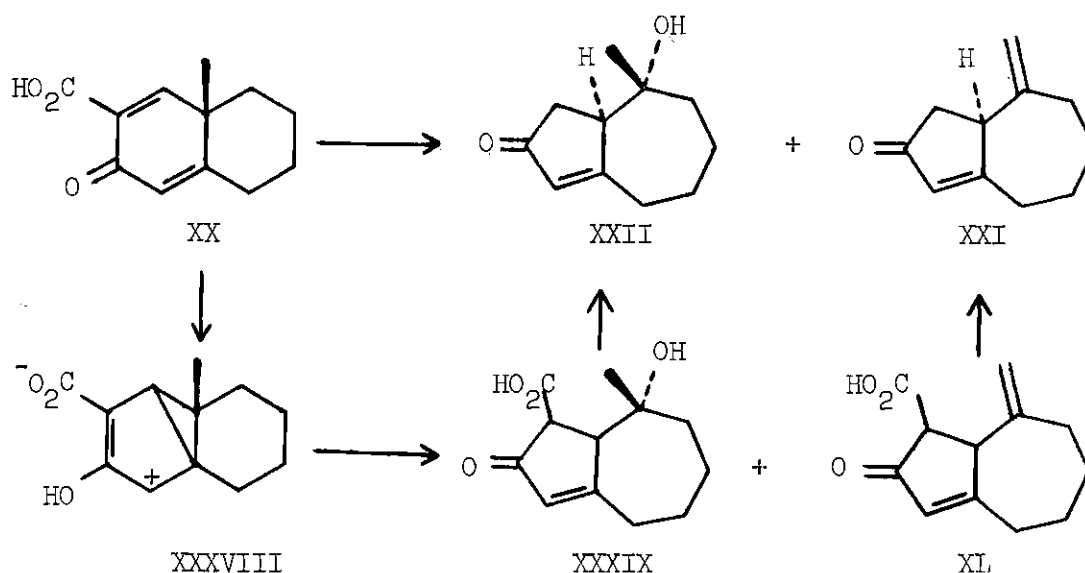
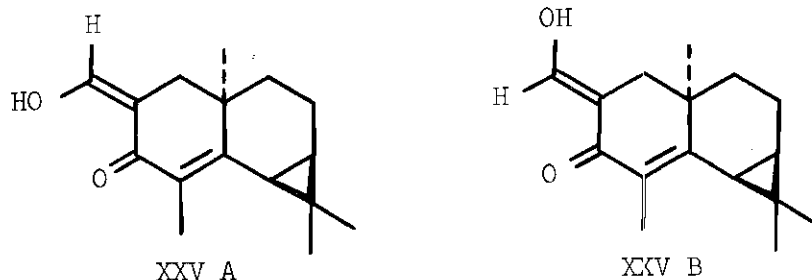


Chart X. Photolysis of a 2-Carboxy Dienone.

It was hoped that a carboxy substituent at C-2 in (-)-dehydro-maalienone would influence the electronic characteristics of the dienone in such a way that rearrangement could be induced without disturbing the cyclopropyl ring. The 2-carboxy derivative was prepared in a straightforward manner in three steps. Introduction of a hydroxymethylene substituent at C-2 was accomplished in good yield on treatment of X with sodium methoxide and ethyl formate in benzene (20). The ir spectrum of the product showed a carbonyl absorption at  $1638\text{ cm}^{-1}$  indicating the presence of an enolized  $\beta$ -diketone (27), but very little absorption for a hydroxyl group. This could be due to extensive hydrogen bonding between the hydroxyl and carbonyl functions. The nmr spectrum of the product showed two singlets totalling one proton at 6.31 and 7.40 ppm. These absorptions

are characteristic of vinyl protons and indicate that the product exists mainly as a mixture of the enol forms XXV A and XXV B.



The 2-hydroxymethylene compound underwent oxidation to the 2-formyl dienone under much milder conditions than were required for the C-2 unsubstituted case. The reaction was complete in three minutes at room temperature, and the yield was over twice that of the unsubstituted dienone. The rate of reaction with DDQ is dependent upon the amount of enol form present in equilibrium with the enone. With the unsubstituted enone some acid is usually added as a catalyst to induce enolization. However, the 2-hydroxymethylene enone actually exists mainly in the enol form and therefore reacts more readily, even in the absence of an acid catalyst, than the simple enone.

The nmr spectra of all of the cyclopropyl enones and dienones involved in this work show relatively large differences in the position of absorption of  $\alpha$ - and  $\beta$ -methyl groups on the three-membered rings. The formyl dienone is a representative example of these compounds. With the three-membered ring oriented  $\beta$  to the B ring,

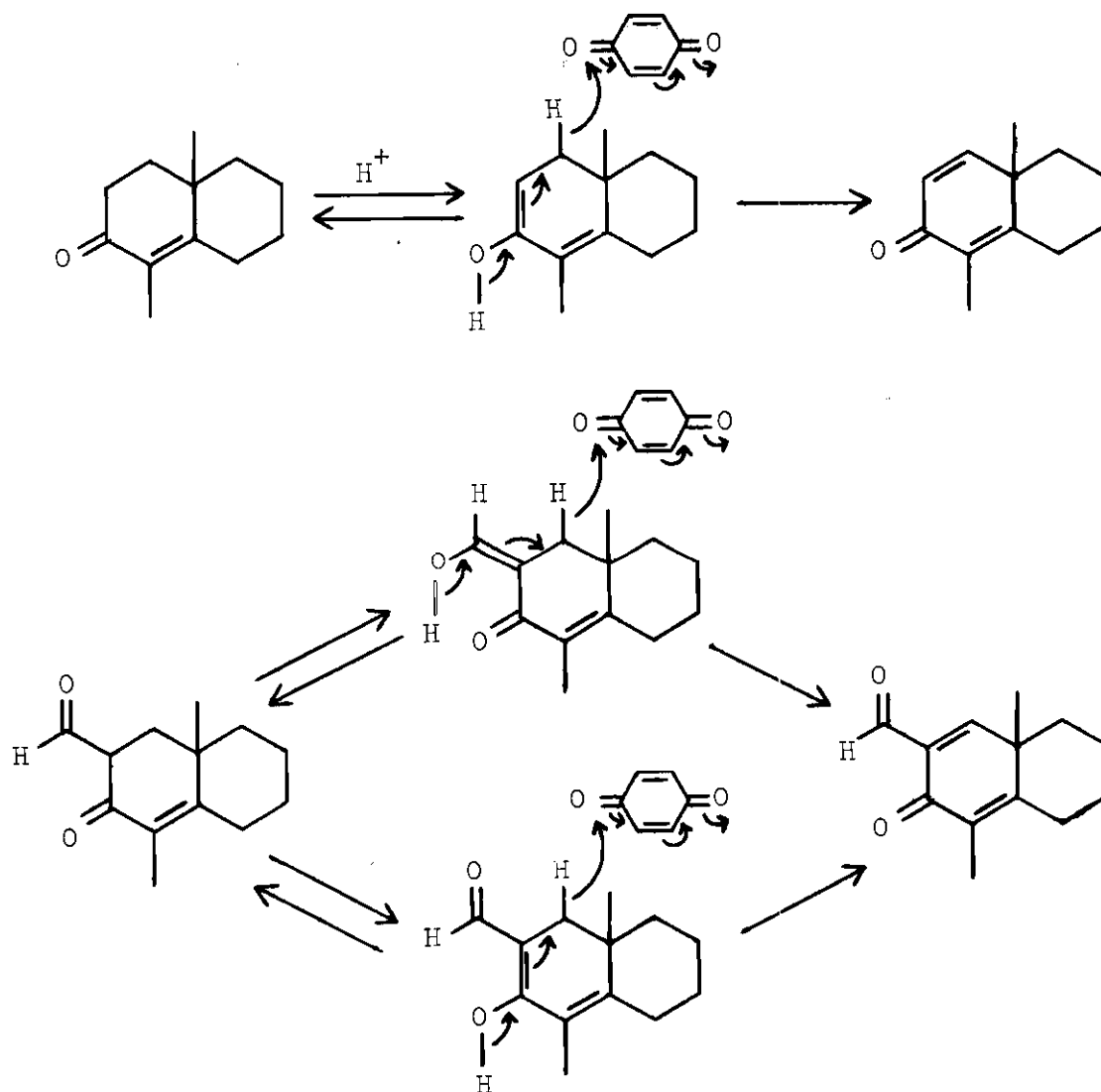


Chart XI. Mechanisms of DDQ Oxidations.

the  $\beta$ -methyl is partially shielded by the  $\pi$  system which causes it to absorb at relatively high field (0.83 ppm). The  $\alpha$ -methyl on the other hand sticks out away from the molecule, and being less shielded it absorbs at lower field (1.23 ppm). The spectrum also shows the vinyl proton at 7.48 ppm and the aldehyde proton downfield at 10.22 ppm. Ir absorptions at 1703 and 1651  $\text{cm}^{-1}$  indicated the presence of two conjugated carbonyl groups.

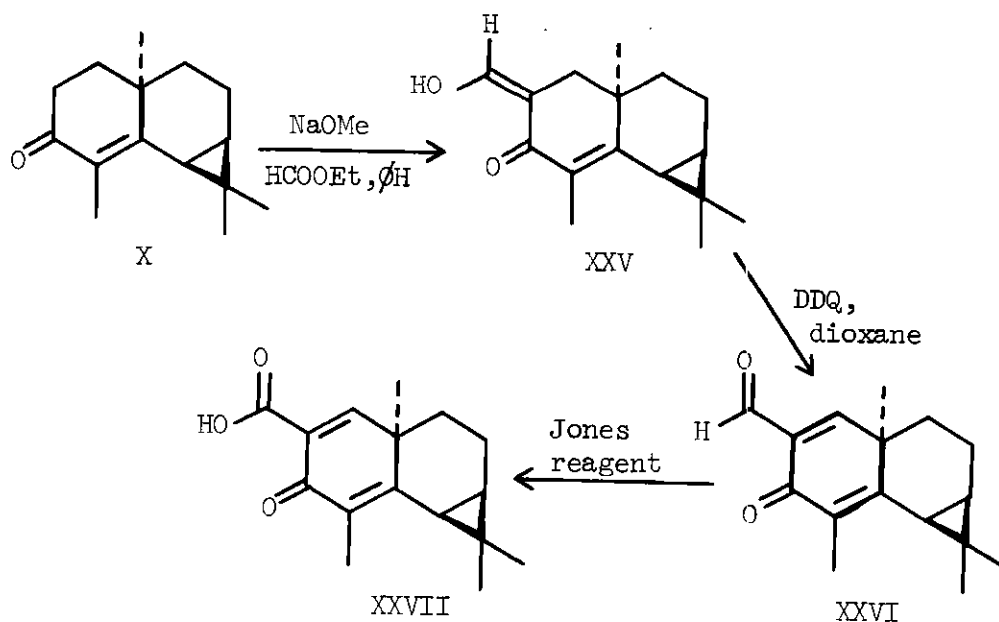
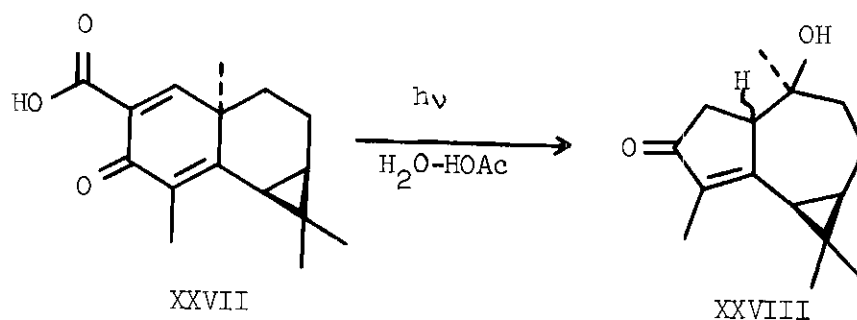


Chart XII. Synthesis of 2-Carboxydehydromaleinone.

Finally treatment of XXVI with Jones reagent gave the desired 2-carboxy dienone XXVII as a crystalline compound melting at 100-2°C. The nmr spectrum of XXVII showed absorptions for the cyclopropyl methyl groups similar to those shown by XXVI and for a vinyl hydrogen

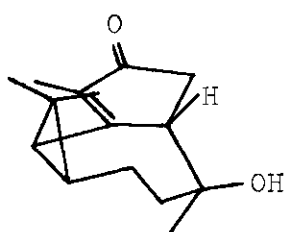
at 8.16 ppm. The carboxyl hydrogen, being very acidic as well as hydrogen bonded, gave a diffuse absorption at 11.84 ppm. Uv maximums occurred at 220 nm ( $\epsilon$  10,300) and 297 nm ( $\epsilon$  4,500). The overall yield of almost 20 percent for the conversion of maalienone into XXVII was just slightly less than the 27 percent yield obtained for the conversion to the unsubstituted dienone.

The 2-carboxy dienone had the correct orientation of the cyclopropyl ring and the 10-methyl group for photochemical conversion into a precursor of (-)-cyclocolorenone. It was hoped that irradiation in aqueous acetic acid would result in the formation of a 5/7-fused hydroxy enone with the three-membered ring closed. After irradiation and isolation of products by chromatography on silica gel, it was found that one major compound was produced in 26 percent yield. This compound, which was shown by spectral evidence to be a hydroxy enone XXVIII, and a small amount of the starting dienone were the only products that could be identified.

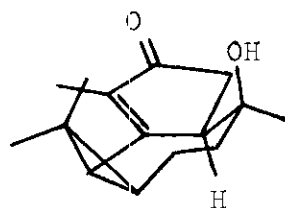


Ir absorptions by XXVIII at 3400 and 1686  $\text{cm}^{-1}$  indicated the presence of a hydroxyl group and an  $\alpha,\beta$ -unsaturated ketone, and the

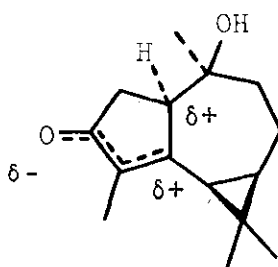
absence of an nmr absorption in the vinyl region indicated that the cyclopropyl ring had remained closed in the rearrangement. However, the nmr absorptions for the methyl groups were not at exactly the same positions as those reported by Streith and Blind, who had prepared this hydroxy enone with the  $1\beta$ -hydrogen by another route (11) (see Chapter I). More significant was the fact that the uv absorption for the photoproduct came at 241 nm -- a considerably shorter wavelength than the 266 nm for the hydroxy enone reported. For this reason it is postulated that the photoproduct formed first in the rearrangement had a  $1\beta$ -hydrogen as it should considering the proposed intermediate for the rearrangement (see Chapter I), but that there was epimerization in the aqueous acidic medium to give the more stable configuration with the  $1\alpha$ -hydrogen in the observed product. As mentioned in Chapter I the stereochemistry of the natural product with cyclopropyl ring and 1-hydrogen both  $\beta$  is such that the bonds forming the three-membered ring are almost parallel to the p orbitals of the conjugated system, and conjugation is thus extended. By examination of models of the two hydroxy enones XXVIII it can be seen that XXVIII A with  $1\beta$ -hydrogen should exhibit a longer wavelength uv absorption and that the product isolated from the photolysis is probably XXVIII B with  $1\alpha$ -hydrogen. Also the hydroxyl group causes an absorption at shorter wavelength (higher energy) than might be expected normally since the partial positive charge induced at C-1 tends to destabilize the partial positive charge present at C-5 in the excited state of the enone.



XXVIII A



XXVIII B

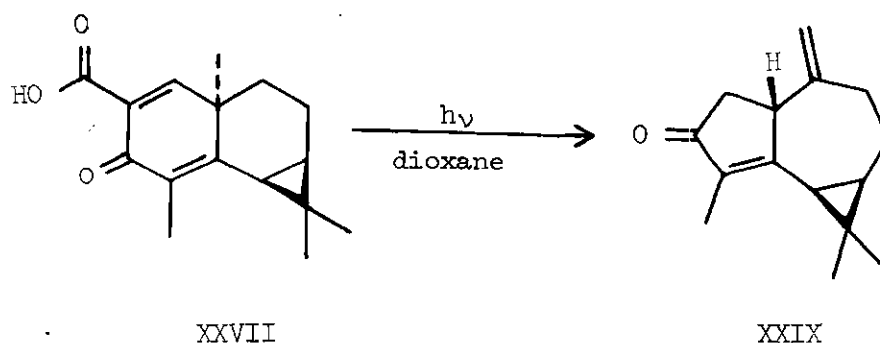


Dehydrations of XXVIII B were attempted in order to determine if an exocyclic double bond could be produced as a means of getting to the natural product. However, since both treatment with thionyl chloride in pyridine at 0°C and treatment with carboxysulfamoyl triethyl ammonium hydroxide inner salt, methyl ester (22) in acetonitrile at 45°C gave no identifiable products, this route to cyclocolorenone was abandoned.

Another irradiation of XXVII was carried out in anhydrous dioxane in the hope that the exo methylene compound XXIX would be produced directly in the photolysis and that there would be no epimerization at C-1. Again only one major product was obtained. Glc and nmr analysis of the crude product showed approximately 80 percent yield of this one component, but after chromatography on

silica gel the product was isolated in only 40 percent yield.

Spectral evidence indicated the presence of an  $\alpha,\beta$ -unsaturated ketone ( $1695\text{ cm}^{-1}$  ir absorption), only the two vinyl hydrogens on the exocyclic double bond ( $4.84$  and  $4.96$  ppm nmr absorptions), and a  $1\beta$ -hydrogen ( $262\text{ nm}$  uv absorption), so XXIX was confirmed as the structure of the photoproduct.



The dienone XXIX has the correct substituents and stereochemistry at the three asymmetric centers for conversion into (-)-cyclocolorenone. Catalytic reduction of the exocyclic double bond from the  $\beta$  face of the molecule would complete the synthesis. Examination of a model of the compound showed that reduction should indeed take place from the desired direction since the seven-membered ring is bent around in a boat-like conformation protecting the bottom side of the exo methylene group. Hydrogenation over palladium on carbon gave complete reduction of the methylene double bond in 40 minutes with no reduction of the conjugated double bond. Again glc analysis of the crude product showed 85 percent yield of one product which was isolated in 40 percent yield by distillation.



The nmr and ir spectra were identical to those of natural cyclocolorenone which were kindly supplied by Professor Büchi and Professor Corbett. A sample of authentic cyclocolorenone was not available for comparison.

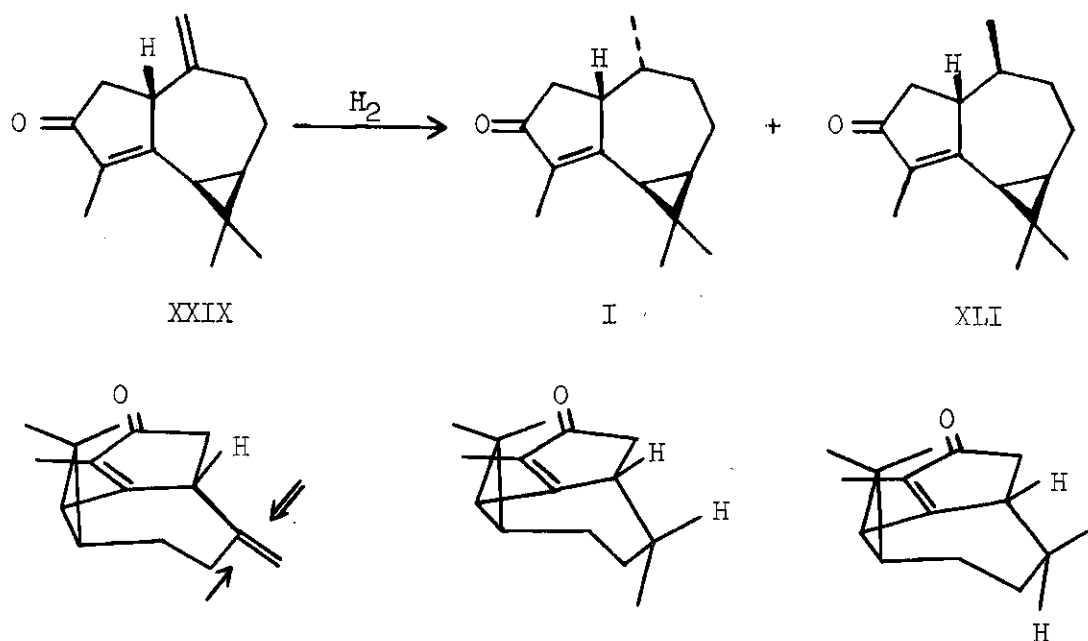


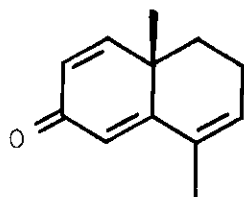
Chart XIII. Reduction of the Photoproduct.

An alternate method of hydrogenation was also used with tris(tri-phenylphosphine)chlororhodium(I) as a homogeneous catalyst (23). The reaction time was much longer than with the heterogeneous catalyst, but the exocyclic double bond was again reduced to the exclusion of the conjugated double bond. With this catalyst, however, the reduction appeared to be less stereoselective. Nmr and glc analyses

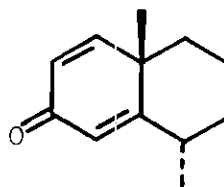
of the crude mixture indicated that a small amount of another dihydro product was present. This product was not isolated and characterized, but the spectral data were consistent with structure XLI, the C-10 epimer of cyclocolorenone which could be produced on reduction of the exocyclic double bond from the  $\alpha$  face of the molecule. This assignment was made since the main difference in the spectra was in the position of absorption of the 10-methyl group in the nmr spectrum. For cyclocolorenone the doublet comes at relatively high field due to larger shielding of the methyl group beneath the enone chromophore. For the C-10 epimer the doublet is downfield in the normal position since the methyl group is sticking out more away from the  $\pi$  system. The higher yield of XLI produced on reduction with the homogeneous catalyst indicated a greater tendency toward attack from the more hindered side of the molecule in this case. This in turn indicated that the homogeneous catalyst has a smaller effective size than the palladium on carbon.

Although a full explanation of the difference in photolabilities of the 2-unsubstituted and 2-carboxy dienones is not possible at present, several conclusions can be drawn. First, if similar mechanisms are involved, it appears that the strain factors associated with the formation of adjacent three-membered rings in the usual intermediate does not prohibit the rearrangement, since the carboxy dienone does rearrange while the cyclopropyl ring remains intact. Second, it may, therefore, be assumed that the cyclopropyl ring affects the electronic nature of the species in such a way that the dienone would be stable to ultraviolet light.

This assumption is supported by correlation with the trienone XLII. In addition to the photostable cyclopropyl ring compounds mentioned, it has been found that the trienone XLII is stable to ultraviolet light (28). Its stability would imply a difference from the analogous photolabile dienone XLIII in the energy and electronic distribution in the ground state species or the photo-excited species with the presence of the additional double bond. And since, as was discussed earlier, the cyclopropyl ring and the 6,7-double bond have somewhat the same effect of extending the conjugation of the system, it follows that they should have similar effects on the energy and electronic character of the species involved in the rearrangement.

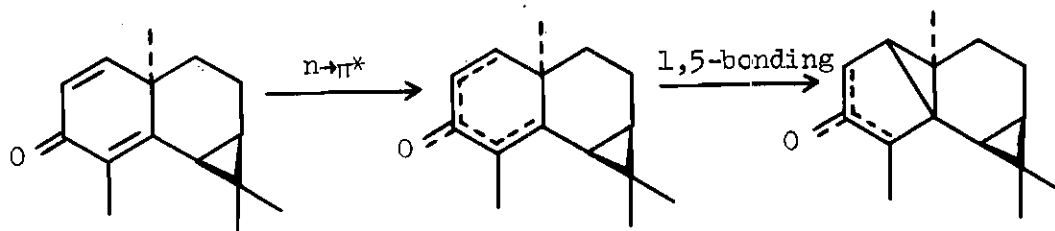


XLII

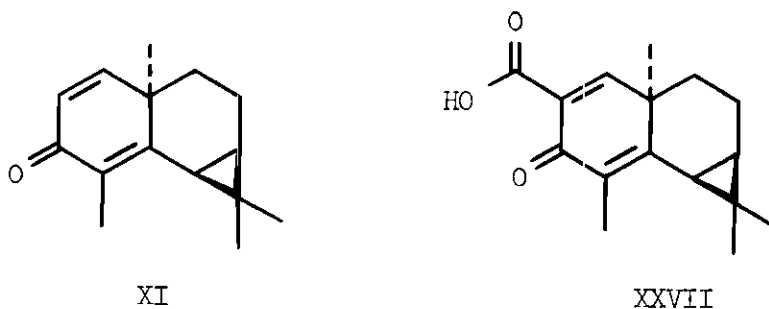


XLIII

In order to be photostable the mechanism for the rearrangement of the dienone (see Chapter I) must break down in one of two places. Either the  $n \rightarrow \pi^*$  electronic transition to the excited species does not occur or the formation of the cyclopropyl intermediate with 1,5-bonding does not take place. The ground state energy level would be lower with the more conjugated system, but the energy barrier in

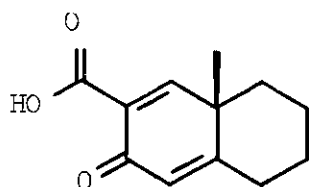


the electronic transition should be about the same since there could be greater delocalization of the radical intermediate and the excited state energy level would also be lower. This supposition has been verified in preliminary studies of the excitation spectra of the stable unsubstituted dienone XI and the reactive carboxy dienone XXVII. In spectra kindly obtained by Professor R. F.

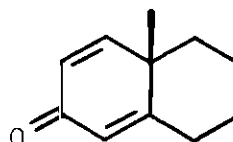


Borkman, both dienones show emissions of similar intensity and similar half-life indicating that the same electronic transitions are taking place and that the stability of XI is due to other factors.

It appears then that the differences in reactivity observed in the photolyses of XI, XXVII, XX, and XLIV arise from differences in the energy barrier involved in the formation of the cyclopropyl

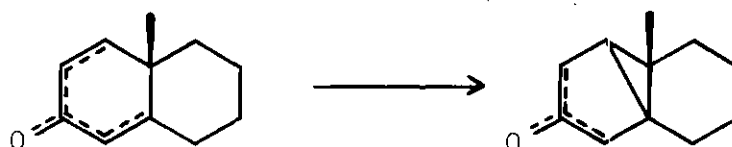


XX



XLIV

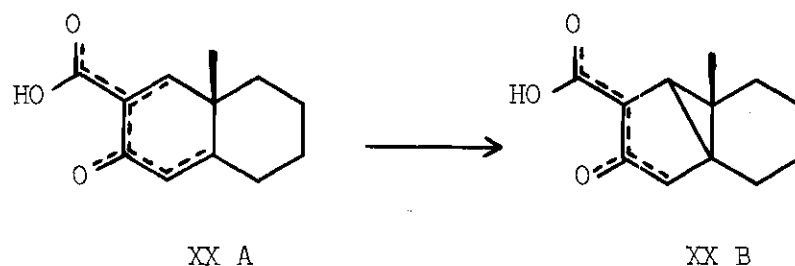
intermediate. In the case of the unsubstituted dienone XLIV an excited state species having a  $\pi$  system extending over six atoms undergoes 1,5-bonding to give another species with the  $\pi$  system over only four atoms. There is a definite barrier to overcome in this process in which 33 percent of the  $\pi$  system is lost, but the rearrangement of this dienone does take place. With the analogous



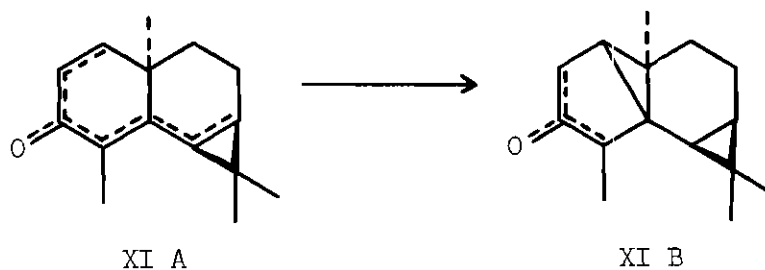
XLIV A

XLIV B

2-carboxy dienone XX the excited state species contains a  $\pi$  system extending over eight atoms, and on bonding the system is reduced to six atoms. Here there is only a 25 percent decrease in the extent of the  $\pi$  system with the carboxyl lowering the energy levels of both species. This analysis would predict the carboxydienone to be more reactive toward ultraviolet light than the unsubstituted dienone, and this is found to be the case (16,17).

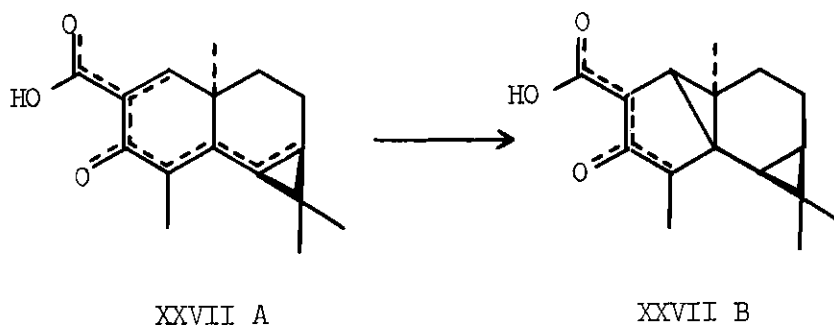


Applying this same reasoning to the cyclopropyl dienone and trienone cases, similar results are obtained. Such a molecule with no carboxyl at C-2 would have an eight-atom  $\pi$  system which, on 1,5-bonding, would produce a four-atom system. Here, since 50



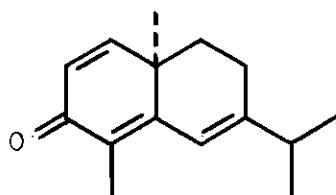
percent of the  $\pi$  system is lost and the additional conjugation lowers the energy of XI A but not XI B, the bonding should be harder to achieve. These dienones and trienones are, in fact, photostable. Addition of a 2-carboxy substituent to a cyclopropyl dienone then should increase the photolability of the molecule. The excited state with a ten-atom  $\pi$  system would produce a cyclopropyl intermediate with a six-atom system. Here there is only a 40 percent decrease in extent of the  $\pi$  system as compared with the 50 percent

decrease for the 2-unsubstituted case, and the energies of both species XXVII A and XXVII B are somewhat lowered by the extended  $\pi$

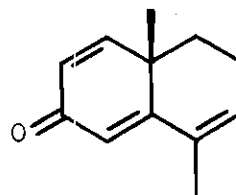


systems. So the 2-carboxy cyclopropyl dienone should be and is more photolabile than the 2-unsubstituted dienone.

Finally, the observed differences in the photolabilities of the trienones XXXIV and XLII may possibly be explained in terms of the same type of argument. The tricyclic radical intermediate from XXXIV may be stabilized just enough by the 4-methyl substituent to form while the 4-unsubstituted intermediate from XLII does not.

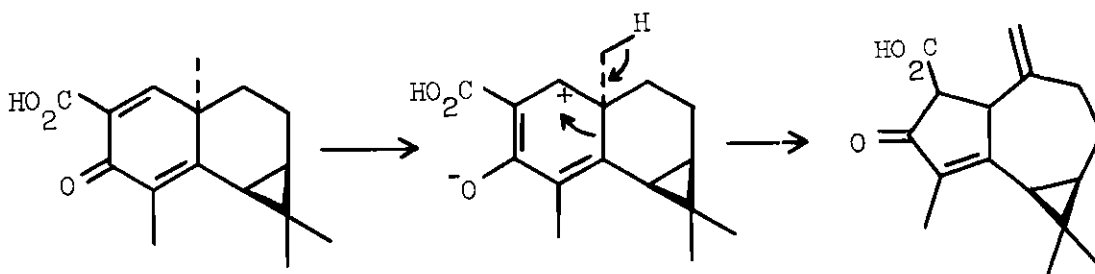


XXXIV



XLII

Although we are inclined to favor the usual mechanism involving the cyclopropyl intermediate discussed above, a possibility exists that the mechanism is changed by the presence of the carboxyl group. A partial positive charge is normally induced at C-1 in the excited state species, and the electron withdrawing carboxyl substituent may enhance this positive charge enough to cause a rearrangement which does not involve the cyclopropyl intermediate.



This mechanism would not involve the strain factors of the previous mechanism.



## CHAPTER V

## CONCLUSIONS

The 6/6-fused cross-conjugated cyclohexadienones XI and XXVII were prepared and their photochemistry was studied. It was found that these dienones were less photolabile than analogous compounds which did not contain the cyclopropyl ring. Rearrangement of XI occurred only in the presence of a sensitizer and was accompanied by opening of the three-membered ring. However, the 5/7-fused system normally expected in the rearrangement of dienones containing C-4 electron donating substituents was obtained. The 2-carboxy substituent was found to activate the system, and XXVII rearranged more easily to the expected 5/7-fused product XXIX.

The photoproduct XXIX was converted into (-)-cyclocolorenone (I) which was identical by nmr, ir, and uv analysis to the naturally occurring compound. Since the structure of cyclocolorenone was already established, this conversion by an unambiguous route constituted a proof of structure of the photoproduct.

The knowledge obtained in the study of the photochemistry of these dienones should be useful in working with other dienones containing the cyclopropyl ring.

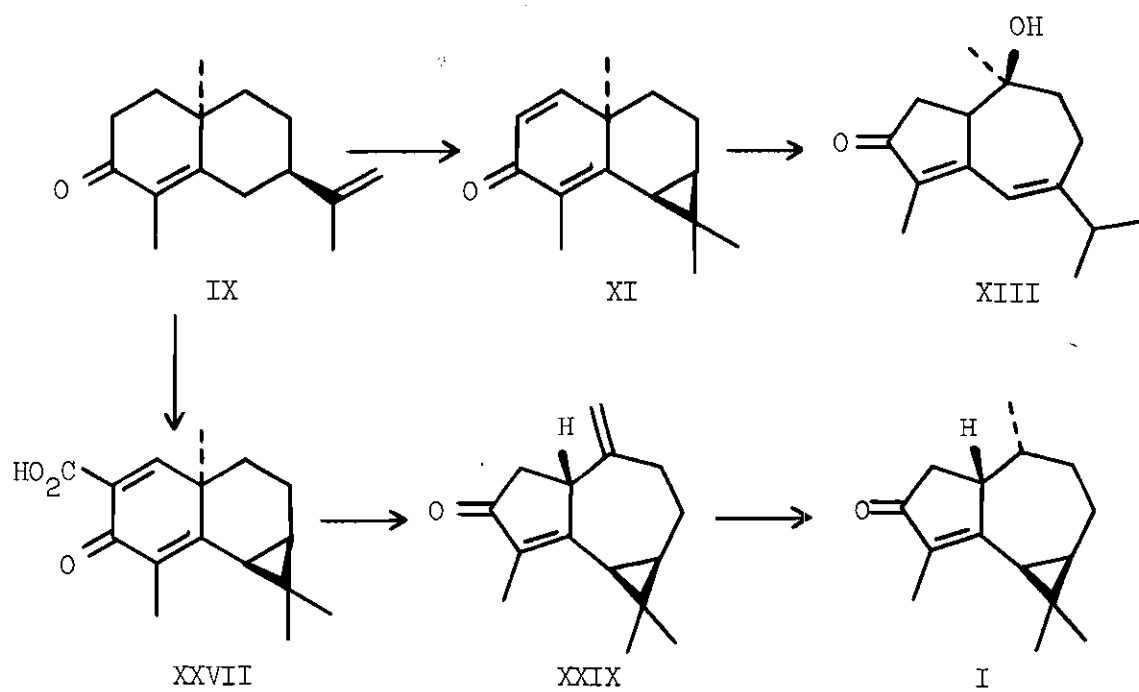
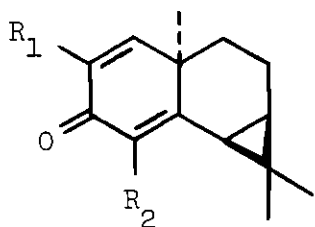


Chart XIV. Summary of Work.

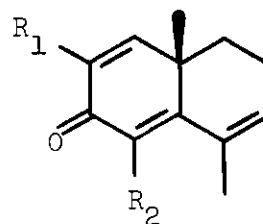
## CHAPTER VI

## RECOMMENDATIONS

Further studies should be undertaken to determine the reason for the difference in the photo-labilities of the 2-unsubstituted and the 2-carboxy dienones. A more exhaustive study of the emission spectra of the dienones should be made, and further photolyses on other dienones should be carried out to determine more fully the effects of carboxy substituents and benzophenone on the ease of rearrangement. For example, the tricyclic dienones XLV should be prepared and irradiated to determine if a 4-carboxy substituent increases the lability of a dienone as a 2-carboxy substituent does. By the same token trienones XLVI B and C should be irradiated to see if the carboxy substituent activates the photostable XLVIA (28). And XLVIA should be irradiated in the presence of benzophenone to see if a sensitizer activates the trienone.



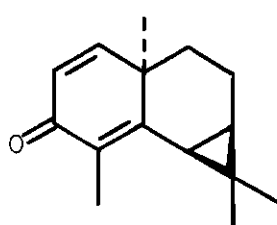
XLV



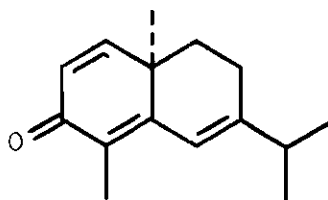
XLVI

- A  $R_1 = R_2 = H$   
 B  $R_1 = COOH, R_2 = H$   
 C  $R_1 = H, R_2 = COOH$

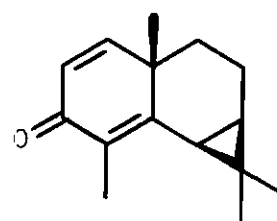
Other photolyses could also be of some interest. Dehydro-maalione (XI) should be irradiated in dioxane in the presence of benzophenone to see if the cyclopropyl ring would open in an inert solvent. Also dehydro- $\beta$ -cyperone (XXXV) should be irradiated in the absence of benzophenone to determine if the sensitizer was necessary for the rearrangement. Finally a dienone such as XLVII should be prepared and irradiated to see if a cyclopropyl ring oriented cis to the 10-methyl causes photostability as the trans oriented ring does.



XI



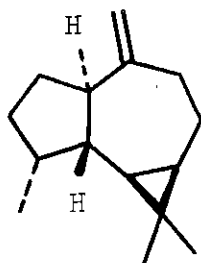
XXXV



XLVII

Since the apparent yields of the photoproduct XXIX and cyclocolorenone (I) as determined by spectra of the crude products is so much greater than that actually isolated, some work should be done on better methods of purification of these compounds.

Attempts should be made to synthesize (+)-aromadendrene (XLVIII) and other naturally occurring compounds related to it (29) by a synthetic route similar to that used in the cyclocolorenone synthesis.



XLVIII

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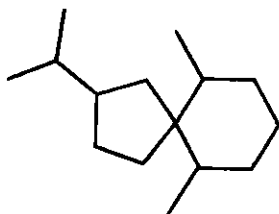
## PART II



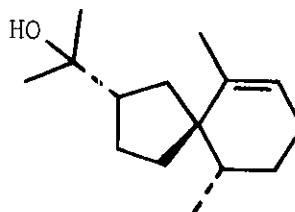
## CHAPTER I

## INTRODUCTION

A number of naturally occurring sesquiterpenes have been found to have the vetispirane skeleton I. Agarospirol (II) was isolated by Bhattacharyya and co-workers, and its physical and chemical properties showed it to be a bicyclic unsaturated tertiary alcohol (1). Degradative experiments established the structure of the spiro[4.5]decane sesquiterpene, and through nmr studies and consideration of its probable biogenesis the stereochemistry of the compound was established (1).



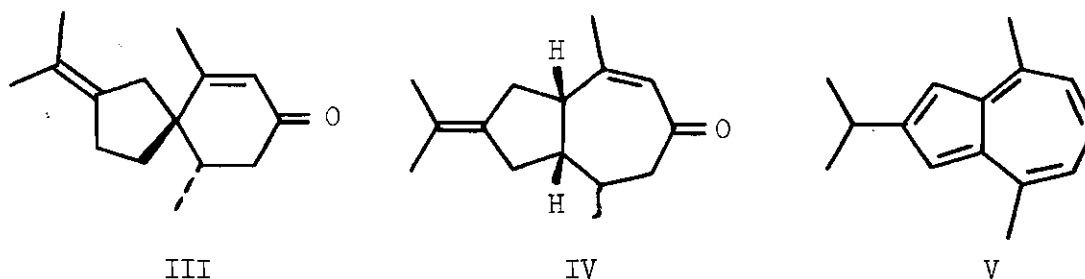
I



II

$\beta$ -vetivone (III) was isolated and studied by Pfau and Plattner (2). However, due to a rearrangement of the ring system during the degradative studies, it was thought until recently that  $\beta$ -vetivone had the hydroazulene structure IV. This rearrangement took place on dehydrogenation of  $\beta$ -vetivone with selenium, and one of the products isolated was vetivazulene (V) (2). The correction was not made until

synthetic work by Marshall showed the inconsistency (3). Before this



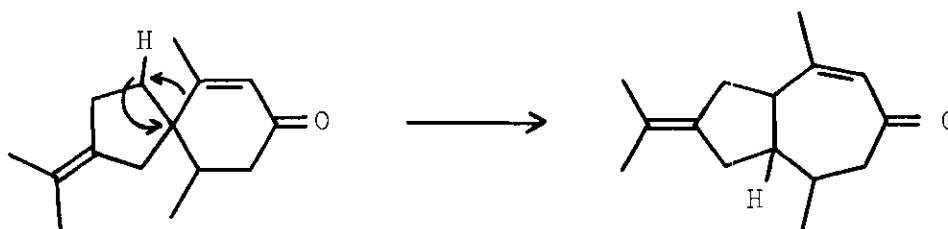
time, however, other sesquiterpenes were discovered and assigned incorrect structures on the basis of their relationship to  $\beta$ -vetivone. Among these were hinesol (4) given the structure VI (5), and  $\alpha$ - and  $\beta$ -isovetivenene, thought to be stereoisomers of the structure VII (6).



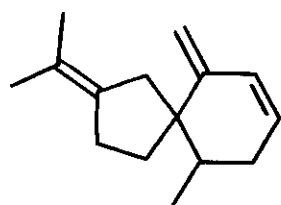
Some questions arose when the ir spectra of the saturated hydrogenation products of the vetivones and that of perhydrovetivazulene differed significantly, but the differences were then attributed to stereoisomerism (6).

The true structures of the spiro[4.5]decanes were finally deduced during preliminary studies into possible syntheses of the

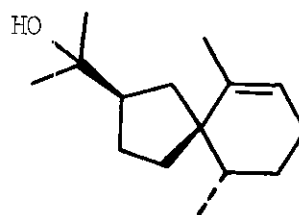
proposed hydroazulenenic structures. Marshall and Andersen found that synthetic hydroazulenenic compounds did not match degradation products which were supposed to have the same structure (3,7). Since the carbonyl absorptions of the natural products and degradation products seemed to indicate the presence of a five-membered ring and a six-membered ring, the spiro[4.5]decane structure was proposed, and the rearrangement was explained by the simple mechanism:



This structure for  $\beta$ -vetivone was supported by the conversions of both the natural product and the known tricyclic ketone VIII into the same spiro hydrocarbon by the routes shown in Chart I. The proposed structures of the isoyetivenenes were thus changed from the hydroazulene VII to the spirodecene IX.



IX



X

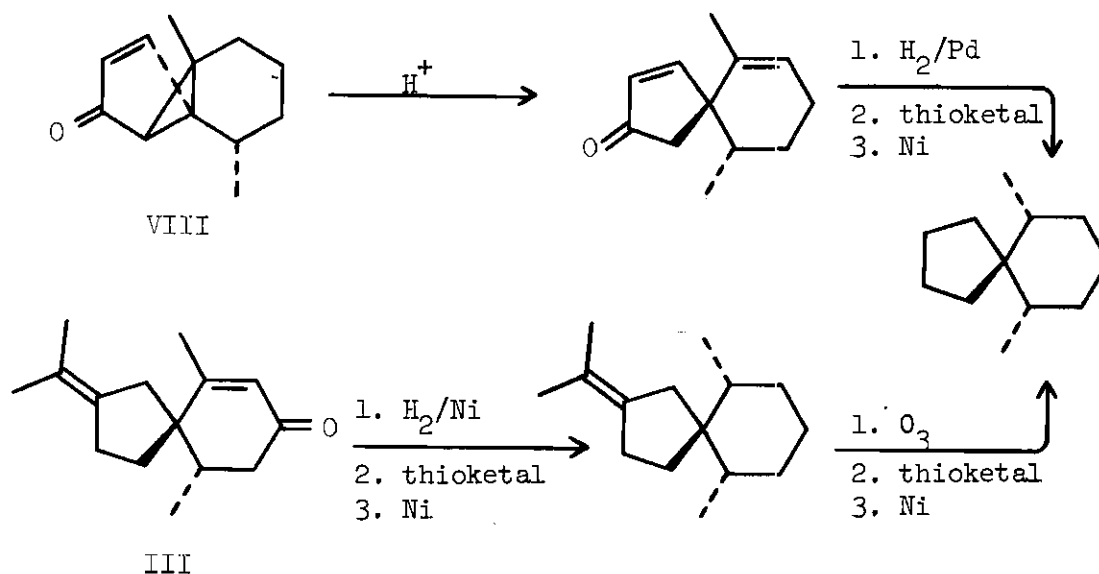
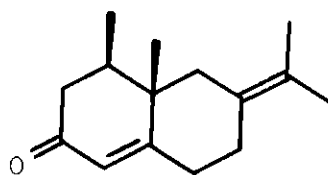


Chart I. Proof of Structure of  $\beta$ -Vetivone.

The absolute stereochemistry of the spiro[4.5]decanes has been determined in general by correlation with hinesol (X), the stereochemistry of which has been proven in an unambiguous total synthesis which will be discussed later (9).

It was originally thought that  $\alpha$ -vetivone was a stereoisomer of structure IV. However, Marshall and de Mayo showed independently that  $\alpha$ -vetivone was neither a hydroazulene derivative nor a spiro[4.5]-decane and assigned it the eremophilane structure XI (10).



XI

The first total synthesis of a vetispirane sesquiterpene was that of  $\beta$ -vetivone by Marshall (11). This synthesis involved the photochemical rearrangement of the 6/6-fused cross-conjugated cyclohexadienone XII and further rearrangement of the tricyclic product in acid to give the [4.5]spiro compound XIII. Reduction of the conjugated double bond and treatment with sodium methoxide and ethyl formate introduced a functional group  $\alpha$  to the carbonyl. In five steps the C-3 carbonyl was removed and the  $\alpha,\beta$ -unsaturated methyl ketone XIV was produced. Three more steps yielded a mixture of hinesol and agarospirol which was finally converted into  $\beta$ -vetivone.

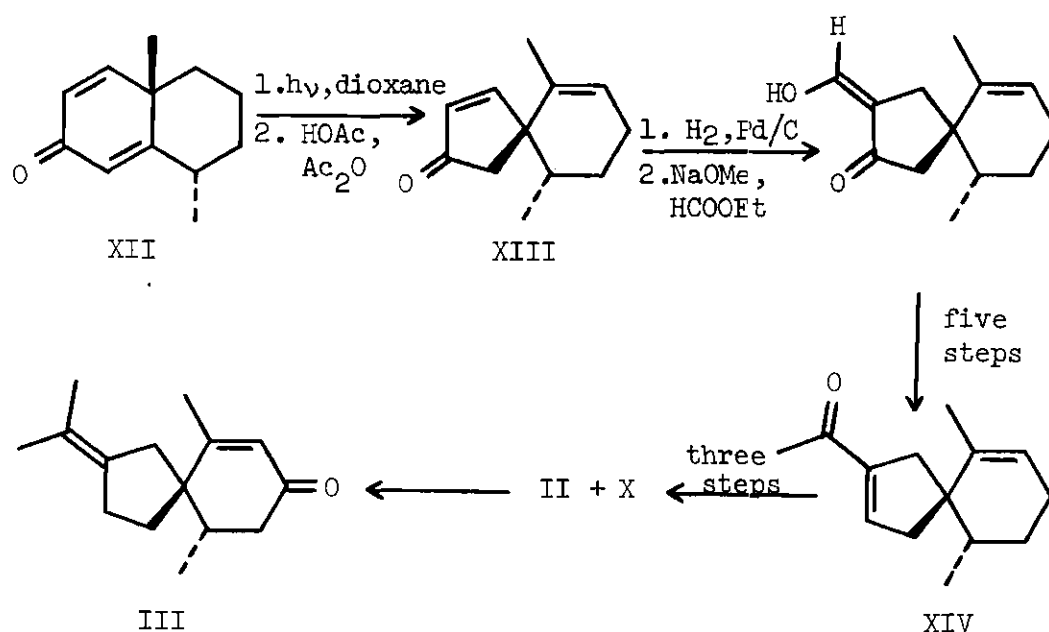


Chart II. Marshall's Synthesis of  $\beta$ -Vetivone.

In another total synthesis of racemic  $\beta$ -vetivone Johnson formed the spiro system in the final step (12). Birch reduction of the

anisole XV, thermal isomerization to give a 1,3-diene, and treatment with methyl acrylate gave the Diels-Alder adduct XVI. Alkylation with ethylene oxide and addition of methyl magnesium bromide to the resulting lactone yielded the diol XVII. Trifluoroacetic acid induced fragmentation of the diol and replacement of the trifluoroacetic grouping with a tosyl group gave the enone XVIII which was in turn treated with sodium hydroxide in aqueous dimethyl sulfoxide to produce the final product via a stereoselective internal alkylation.

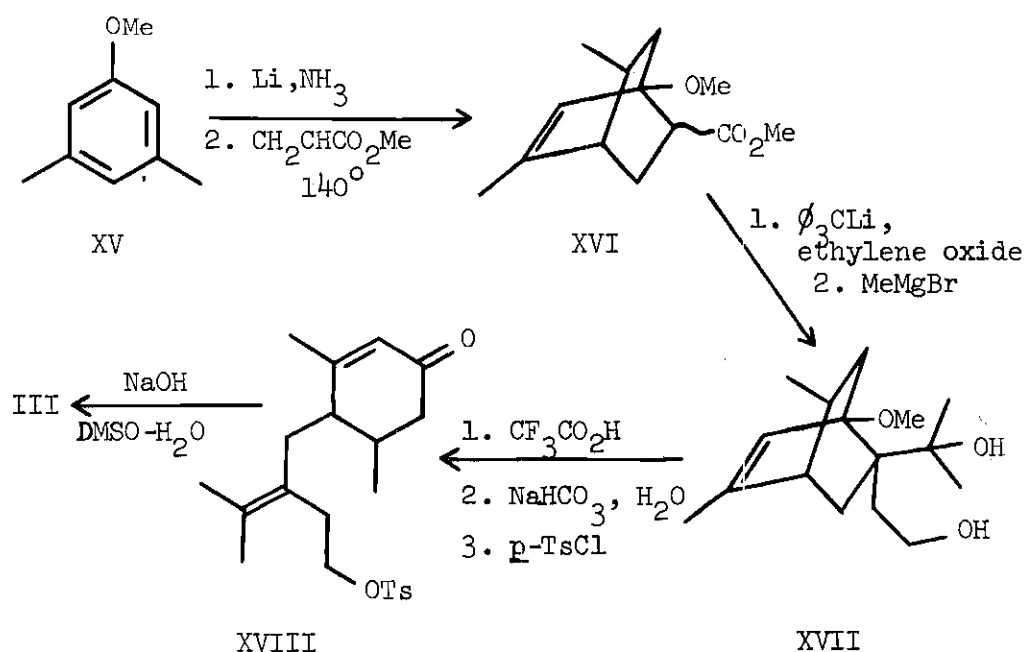


Chart III. Johnson's Synthesis of  $\beta$ -Vetivone.

Deslongchamps has developed a synthetic route to the vetispirenes (13). In eight steps the keto ester XIX was converted into the diazo ketone XX which, on treatment with copper in benzene, gives rise to a

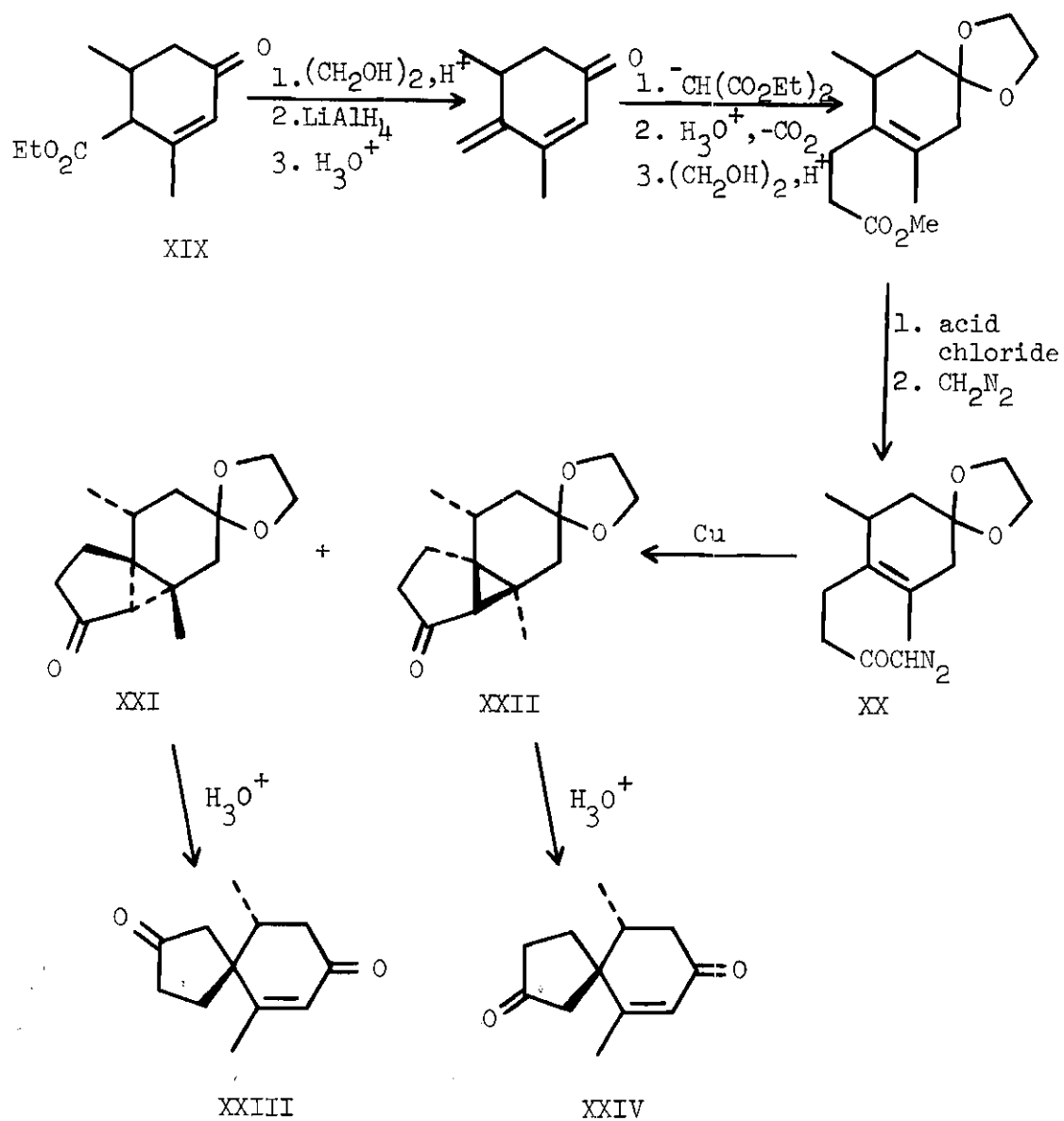


Chart IV. Deslongchamps' Route to Vetispirenes.

mixture of the cyclopropyl ketones XXI and XXII. The cyclopropyl ring undergoes cleavage in aqueous acid to give the spiro[4.5]-decenediones XXIII and XXIV. When the appropriate side chains are introduced into the cyclopropyl ketones, this cleavage results in production of the natural products, (see Chart IV).

Hinesol was synthesized by Marshall and Brady (10) and the synthesis finally established the stereochemistry of the isopropylol grouping in this natural product. The starting tricyclic dienone, with the spiro[4.5]-decane structure already present as part of the ring system was methylated on treatment with lithium dimethylcopper. Enol acetylation and borohydride reduction of the product led to the alcohol XXV. Acetylation and chromic acid oxidation gave an acetoxy enone which lost acetic acid on treatment with mineral acid. Partial hydrogenation of dienone XXVI followed by reduction of the enone with lithium tri-*t*-butoxyaluminumhydride and epoxidation with *m*-chloroperbenzoic acid produced the epoxy alcohol XXVII. Successive treatment with lithium aluminum hydride and methanesulfonyl chloride gave the hydroxy mesylate XXVIII which yielded the spiro[4.5]decane XXIX in base. In three steps the epoxy acetate XXX was produced, and three more steps yielded acetate XXXI. Reduction of the acetate and Jones oxidation of the resulting secondary alcohol gave the methyl ketone XXXII. Finally treatment with methyl lithium resulted in the production of racemic hinesol X, (see Chart V).

Recently a new sesquiterpene triene having the vetispirane skeleton has been isolated by Andersen, Falcone, and Syrdal as one



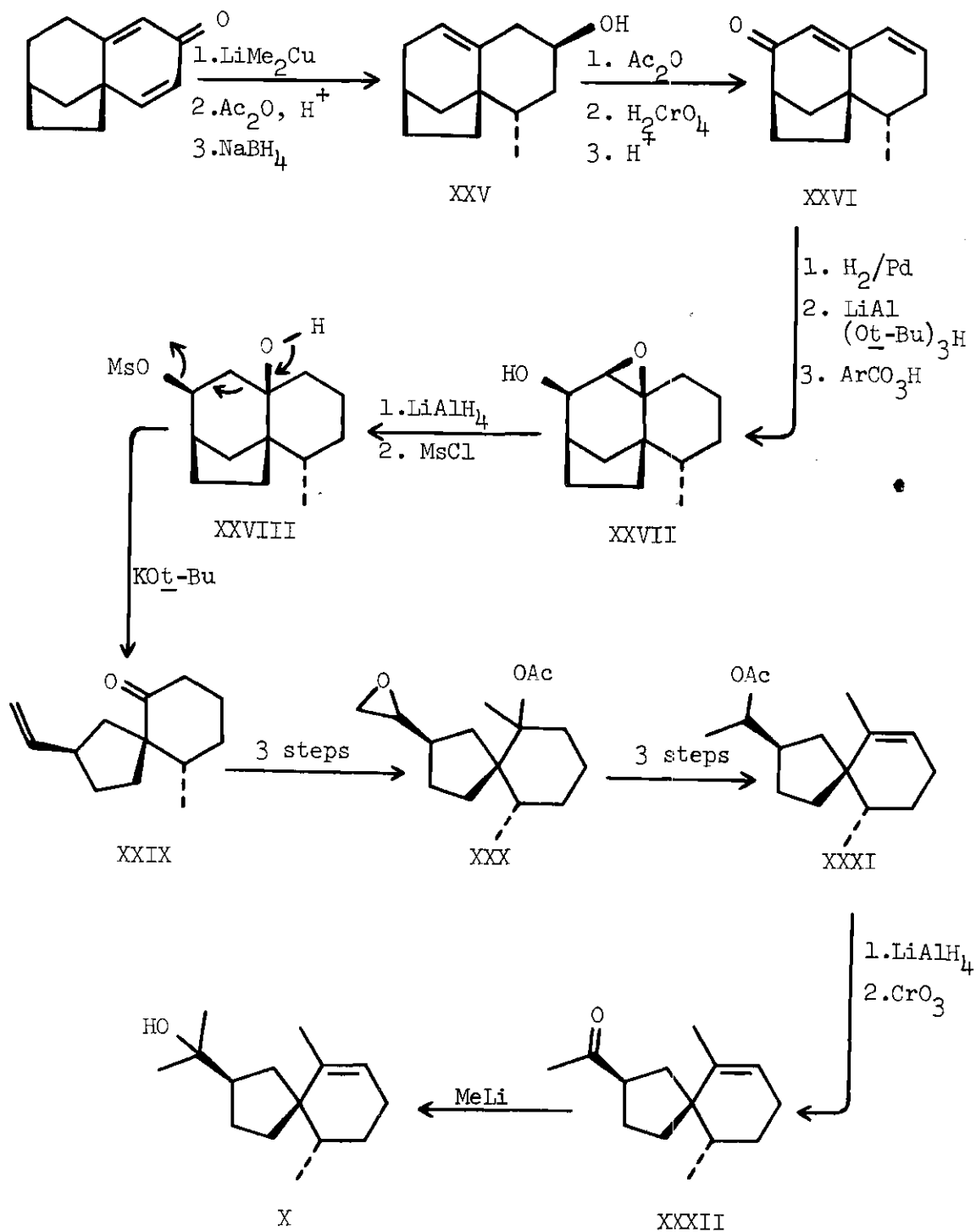
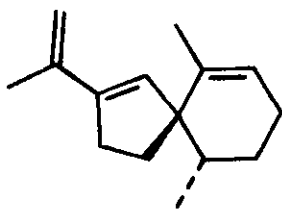


Chart V. Synthesis of Hinesol by Marshall and Brady.

of many constituents of vetiver oil (14). This compound,  $\alpha$ -vetis-pirene, was identified by hydrogenation to vetispiranes and by nmr and nmdr experiments and has been assigned the structure XXXIII.



XXXIII

The purpose of this research was to synthesize this new triene by a route which, with slight modification, could also provide for a more facile synthesis of  $\beta$ -vetivone. To this end a synthetic route utilizing the photochemical rearrangement of a 6/6-fused cross-conjugated cyclohexadienone to give the necessary [4.5]spiro system was chosen. It has been well documented that irradiations of cyclohexadienones of type A in aqueous acidic media produce hydroxy enones of types B or C, and the rearrangements have been found to be stereospecific (15). According to the mechanism proposed by Zimmerman and coworkers (16) the dienone undergoes an  $n \rightarrow \pi^*$  electronic transition to the singlet excited state and intersystem crossing to give the triplet excited state. This is followed by 1,5-bonding to give a diradical which can be represented by resonance forms D and E. Electron demotion and protonation results in the mesoionic species represented by F and G. The electronic characteristics of the substituents  $R_1$  and  $R_2$  then determine which is the more important

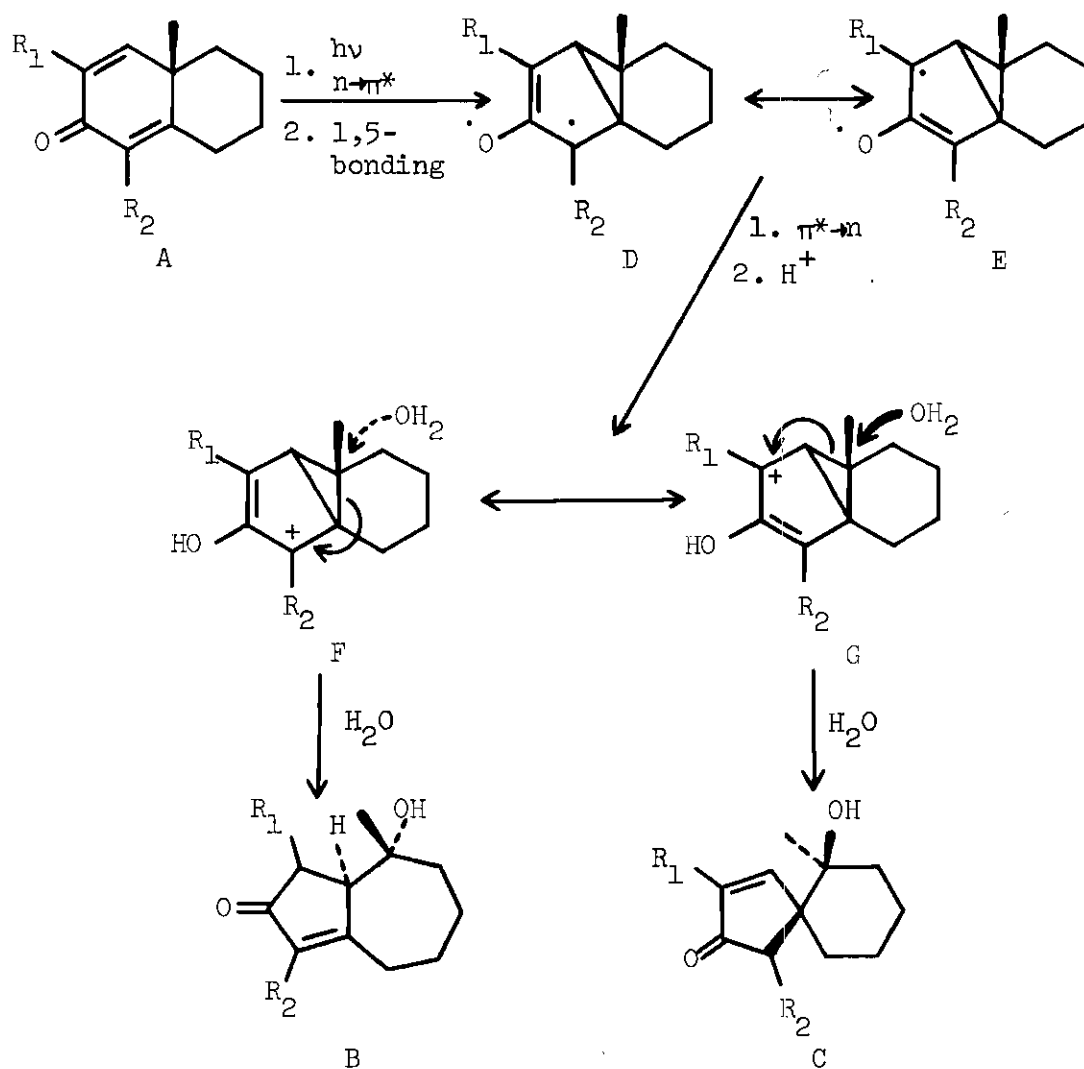


Chart VI. Mechanism of Photochemical Rearrangements of Cross-Conjugated Cyclohexdienones.

resonance structure and hence which product predominates - the 5/7-fused hydroxy enone B or the [4.5]spiro hydroxy enone C, (see Chart VI).

In Marshall's synthesis a new functional group was introduced  $\alpha$  to the carbonyl group after rearrangement to the spiro system (11). An attractive route to both  $\beta$ -vetivone and  $\alpha$ -vetispiroene appeared to be through a dienone which already had a functional group at C-2. The 2-methoxy dienone XXXV prepared from 3-keto-6,10-dimethyl- $\Delta^4$ -octahydronaphthalene (XXXIV) was therefore chosen as starting material for two reasons. The electron donating methoxy substituent would stabilize the positive charge at C-2 in the intermediate carbonium ion of the photo reaction and would therefore provide for a more facile rearrangement to a spiro system. And the enol ether function could then be easily hydrolyzed at an appropriate point in the synthesis to give a carbonyl group at C-2 and thus provide a method of adding a side chain at that position.

Irradiation of XXXV in glacial acetic acid gave the expected acetoxy ketone XXXVI in good yield with the correct stereochemistry for conversion to the natural products, (see Chart VII). In several steps the photoproduct was converted into the key intermediate ketone XLI which had been prepared earlier by Dawson by a similar route (19). From this ketone several natural products may be produced. Introduction of an isopropenyl side chain at C-2 in XLI could lead to the synthesis of  $\alpha$ -vetispiroene (XXXVIII). Formation of the methyl ketone XLVI with an acetyl group at C-2 would constitute a formal synthesis of  $\beta$ -vetivone

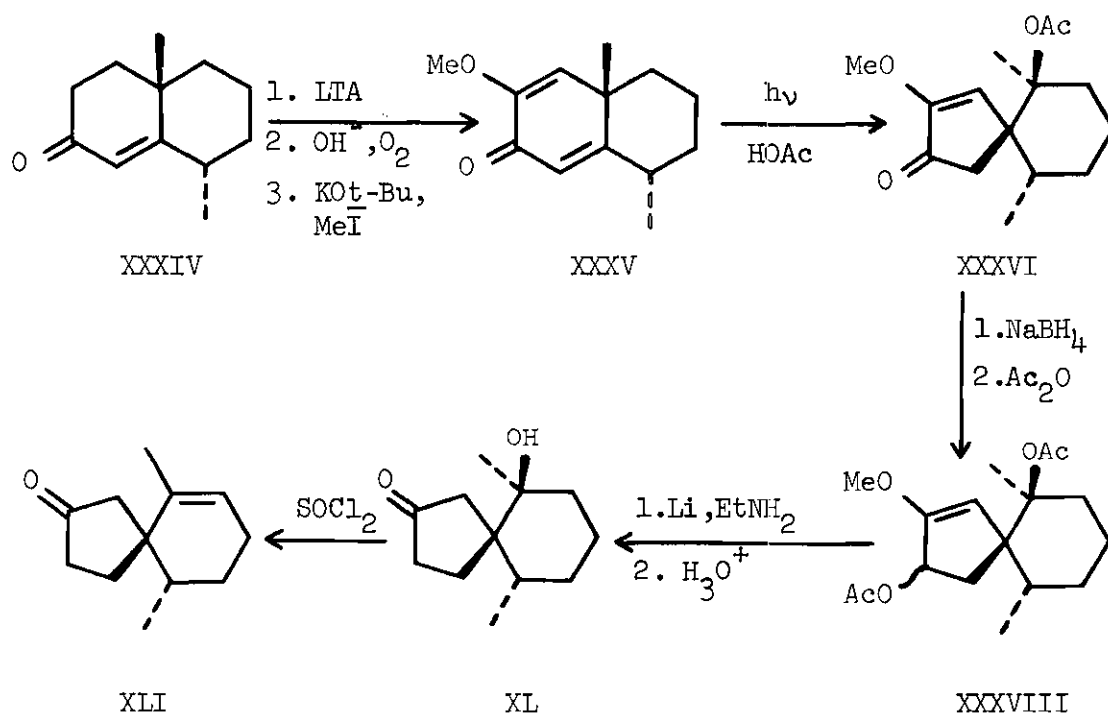
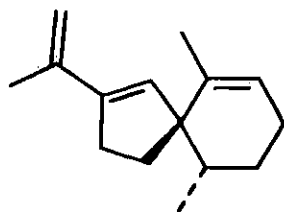
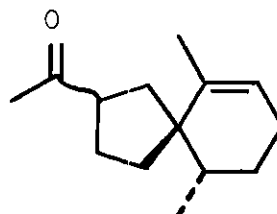


Chart VII. Synthesis of 2-Keto-6,10 $\alpha$ -dimethyl[4.5]-spirodecene-6.

since XLVI was an intermediate in Marshall's synthesis (11).



XXXIII



XLVI

## CHAPTER II

## INSTRUMENTATION AND EQUIPMENT

When required for a reaction, a nitrogen atmosphere was established using an apparatus similar to that described by Johnson (17). Removal of solvents in vacuo was done using a Büchi Rotavapor rotary evaporator. A Hanovia 450-watt high pressure mercury lamp in a Pyrex apparatus similar to that described by Kropp and Erman (18) was the light source for the irradiations. A slow stream of dried, prepurified nitrogen was bubbled through the solution for 10 minutes prior to and during all irradiations for deoxygenation and agitation of the solution. Column chromatographies were carried out using Grace grade 923, 100-200 mesh silica gel in the ratio of about 25g silica gel per gram of mixture. Anhydrous magnesium sulfate was used as drying agent in reaction workups.

Infrared spectra were obtained using a Perkin-Elmer Model 137 or 457 recording spectrophotometer. For spectra run with a solvent, 0.1 mm sodium chloride cells were used. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or A-60D nuclear magnetic resonance spectrometer. Tetramethyl silane was used as an internal standard and the chemical shifts are reported in ppm downfield from it. The abbreviations s, d, t, q and m refer respectively to singlet, doublet, triplet, quartet and multiplet;

coupling constants ( $J$ ) are given in Hz. Ultraviolet spectra were obtained using a Cary Model 14 or a Beckman Model DB-GT recording spectrophotometer using one centimeter balanced cells; 95 percent ethanol was the solvent. Mass spectral data were obtained on a Varian Associates Model M-66 medium resolution mass spectrometer with a 70 electron volt source. Gas chromatographic analyses were done using a Perkin-Elmer Model 881 flame ionization gas chromatograph using a 6 foot by 1/8 inch stainless steel column packed with 10 percent K-20M Carbowax on 60/80 Chromasorb W HMDS with a temperature program of 100° to 200°C at 12 degrees per minute, or a 6 foot by 1/8 inch stainless steel column packed with 10 percent SE-30 on 80/100 Chromasorb W HMDS with a temperature program of 100° to 225°C at 12 degrees per minute. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points are uncorrected. Carbon and hydrogen analyses were performed by either Galbraith Laboratories, Knoxville, Tennessee, or Atlantic Microlab, Inc., Atlanta, Georgia.



## CHAPTER III

## EXPERIMENTAL

Irradiation of 2-Methoxy-3-keto-6,10-dimethyl-  
 $\Delta^{1,4}$ -hexahydronaphthalene (XXXV)

The 2-methoxy dienone XXXV was prepared as previously described by Dawson (19). A solution of 1.00 g (0.0049 mole) of XXXV in 290 ml of glacial acetic acid (freshly distilled from molecular sieves) was irradiated with a 450-watt high pressure mercury lamp for three hours using a Pyrex probe. The solution was washed into a 500 ml round-bottom flask with benzene and frozen, and the solvents were removed by lyophilization to leave light tan crystals. Recrystallization from ether gave 1.15 g (89 percent) of XXXVI as white crystals: mp 124°C; ir ( $\text{CHCl}_3$ ) 1720 (ester C=O), 1710 ( $\alpha,\beta$ -unsaturated C=O), 1626 (conjugated C=C), 1460, 1370, 1255, 1222, 1169, 1128, 1024, 977, 940 and 755  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.72 (d,  $J = 6.5$  Hz, 3H, 10- $\text{CH}_3$ ), 1.37 (s, 3H, 6- $\text{CH}_3$ ), 2.03 (s, 3H, 6-OAc), 2.16 and 2.69 (AB quartet,  $J_{AB} = 19.5$  Hz, 2H, 4-H), 3.77 (s, 3H, 2- $\text{OCH}_3$ ), and 6.22 (s, 1H, 1-H); mass spectrum (70 eV)  $m/e$  266 ( $M^+$ ), 224 ( $M^+ - \text{CH}_2\text{C=O}$ ), EMD 266.157 (Calculated: 266.152).

Anal. Calculated for  $\text{C}_{15}\text{H}_{22}\text{O}_4$ : C, 67.67; H, 8.27. Found: C, 67.52; H, 8.35.

2-Methoxy-3-hydroxy-6 $\alpha$ ,10 $\alpha$ -dimethyl-6 $\beta$ -  
acetoxy[4.5]spirodecene-1 (XXXVII)

A solution of 6.04 g (0.0227 mole) of acetoxy ketone XXXVI and 0.863 g (0.0228 mole) of sodium borohydride in 60 ml of absolute ethanol was stirred in a 100 ml round-bottom flask at room temperature for 48 hours. Acetone (5 ml) was added, and the solution was stirred two hours. The solvents were removed in vacuo, and 100 ml each of ether and water were added to the residue. The layers were separated, the aqueous layer was extracted several times with 20 ml portions of ether, and the combined organic layers were washed with water and dried. Removal of the solvent in vacuo afforded 5.95 g (98 percent) of a mixture of alcohols XXXVII as white crystals. Recrystallization from ether gave an analytical sample: mp 80-90°C; ir (CHCl<sub>3</sub>) 3420 (OH), 1725 (ester C=O), 1648 (C=C), 1447, 1366, 1250, 1168, 1143, 1061, 1040, 827 and 756 cm<sup>-1</sup>; nmr (CDCl<sub>3</sub>)  $\delta$  0.70 and 0.85 (2d, J = 6.5 Hz, 3H, 10-CH<sub>3</sub>); 1.33 and 1.47 (2s, 3H, 6-CH<sub>3</sub>), 1.99 and 2.01 (2s, 3H, 6-OAc), 3.67 (s, 3H, 2-OCH<sub>3</sub>), 4.43 and 4.46 (2s, 1H, 1-H), and 4.57 (d of d, J = 7.5, 13.5 Hz, 1H, 3-H); mass spectrum (70 eV) m/e 268 (M<sup>+</sup>), EMD 268.163 (Calculated: 268.167).

Anal. Calculated for C<sub>15</sub>H<sub>24</sub>O<sub>4</sub>: C, 67.16; H, 8.96. Found: C, 67.23; H, 9.02.

2-Methoxy-3,6 $\beta$ -diacetoxy-6 $\alpha$ ,10 $\alpha$ -dimethyl[4.5]spirodecene-1 (XXXVIII)

A solution of 2.78 g (0.0104 mole) of XXXVII in 40 ml of dry pyridine in a 100 ml round-bottom flask with a nitrogen atmosphere was treated with 8 g (0.0784 mole) of acetic anhydride, and the solution was

stirred at room temperature for 20 hours. The reaction mixture was then cooled to 0°C, 16 ml of water was added carefully, and stirring was continued for two hours. The mixture was then poured into 100 ml of ether, the layers were separated, and the aqueous layer was extracted with 50 ml of ether. The combined organic layers were washed with water and dried, and the solvents were removed in vacuo leaving 3.3 g of pale yellow oil which was shown by glc analysis to be greater than 95 percent diacetate XXXVIII. Chromatography on 60 g of silica gel using hexane-ether as eluent afforded 2.66 g (83 percent) of a mixture of epimers of the diacetate (20 percent ether in hexane): ir (film) 1730 (ester C=O), 1650 (C=C), 1446, 1369, 1245, 1170, 1145, 1033, 943 and 831  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ ) 0.72 and 0.81 (2d,  $J = 6$  Hz, 3H, 10- $\text{CH}_3$ ), 1.32 and 1.40 (2s, 3H, 6- $\text{CH}_3$ ), 1.93 and 1.97 (2s, 6H, 3-OAc and 10-OAc), 3.63 (s, 3H, 2-O $\text{CH}_3$ ), 4.60 (s, 1H, 1-H), and 5.47 (d of d,  $J = 4, 4$  Hz, 1H, 3-H).

Anal. Calculated for  $\text{C}_{17}\text{H}_{26}\text{O}_5$ : C, 65.81; H, 8.39. Found: C, 65.99; H, 8.36.

2-Methoxy-6 $\beta$ -hydroxy-6 $\alpha$ ,10 $\alpha$ -dimethyl[4.5]spirodecene-1 (XXXIX)

In a 250 ml round-bottom flask equipped with magnetic stirrer, dropping funnel, and dry ice condenser and having a nitrogen atmosphere, 125 ml of ethylamine (freshly distilled from lithium) was collected. The ethylamine was cooled to -78°C in a dry ice acetone bath, and to it was added a solution of 1.00 g (0.00323 mole) of XXXVIII and 0.239 g (0.00323 mole) of dry t-butyl alcohol in 25 ml of dry ether. Then 0.1355 g (0.0194 mole) of lithium was added in small, freshly cut pieces.

The mixture was stirred for 1.5 hours, at which time the blue color of the lithium in ethylamine solution persisted. After five minutes additional stirring, the mixture was filtered quickly through glass wool into a flask containing 1 g of solid ammonium chloride, and the flask and funnel were rinsed with dry ether. The solvents were removed in vacuo, 50 ml each of ether and water were added to the residue, and the layers were separated. The aqueous layer was extracted with 50 ml of ether, the combined organic layers were washed with brine and dried, and the ether was removed to leave 0.64 g of an oil which was shown by nmr and glc analysis (Carbowax column) to be a 2:1 mixture of the desired hydroxy compound XXXIX and the compound resulting from reductive fission of the tertiary acetoxyl group. The mixture showed the following spectral properties: ir (film) 3460 (OH), 1649 (C=C), 1460, 1365, 1226, 1036, 920 and 805  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.78 (d,  $J = 6$  Hz, 6- $\text{CH}_3$  of LIV and 10- $\text{CH}_3$ ), 1.09 (s, 6- $\text{CH}_3$  of XXXIX), 3.61 (s, 3H, 2- $\text{OCH}_3$ ), and 4.31 (s, 1H, 1-H). The crude mixture was utilized directly in the next step.

2-Keto-6 $\beta$ -hydroxy-6 $\alpha$ ,10 $\alpha$ -dimethyl[4.5]spirodecane (XL)

A mixture of 0.51 g (0.00243 mole) of the crude mixture from above and 0.11 g (0.00122 mole) of oxalic acid in 22 ml of 60 percent aqueous methanol was stirred at room temperature for 0.5 hours, and 12 ml of saturated sodium bicarbonate was then added. The mixture was extracted with 50 ml of 1:1 benzene-ether, the organic extracts were washed and dried, and the solvents were removed to leave 0.466 g of a yellow oil. Chromatography on silica gel using hexane-ether as

eluent afforded 0.151 g of LVII (10 percent ether in hexane) and 0.227 g (43 percent) of XL (25 percent ether in hexane): ir (film) 3470 (OH), 1735 (C=O), 1476, 1458, 1406, 1378, 1254, 1170, 1072 and 919  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.83 (d,  $J = 6.5$  Hz, 3H, 10- $\text{CH}_3$ ), 1.15 (s, 3H, 6- $\text{CH}_3$ ), and 2.93 (s, 1H, 6-OH).

Anal. Calculated for  $\text{C}_{12}\text{H}_{20}\text{O}_2$ : C, 73.47; H, 10.20. Found: C, 73.26; H, 10.37.

Spectral data for the ketone LVII were: ir (film) 1740 (C=O), 1458, 1405, 1378, 1246 and 1159  $\text{cm}^{-1}$ ; nmr ( $\text{CDCl}_3$ )  $\delta$  0.86 (d,  $J = 5.5$  Hz, 6H, 6- and 10- $\text{CH}_3$ 's).

2-Keto-6,10 $\alpha$ -dimethyl[4.5]spirodecane-6 (XLI)

A solution of 0.224 g (0.00114 mole) of the hydroxy ketone XL in 4 ml of dry pyridine was placed in a 10 ml round-bottom flask under nitrogen and was cooled to 0°C in an ice-salt bath. The solution was then treated with 0.5 ml of thionyl chloride dropwise while keeping the temperature between -2 and 3°C. After the addition was complete the solution was stirred at 0°C for 75 minutes, and 6 ml of water was then added dropwise keeping the temperature of the reaction mixture between 5 and 15°C. The mixture was extracted well with 50 ml of ether, the extracts were washed with brine and dried, and the ether was removed to give 0.124 g (61 percent) of the ketone XLI. Distillation using a micro Hickman apparatus afforded an analytical sample: bp 83°C (bath temperature) (0.7 mm Hg); ir (film) 1742 (C=O), 1450, 1407, 1377, 1159, 899 and 799  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  0.90 (d,  $J = 6$  Hz, 3H, 10- $\text{CH}_3$ ), 1.65 (d,  $J = 1.5$  Hz, 3H, 6- $\text{CH}_3$ ) and 5.37 (s,  $w_h = 8$  Hz, 1H, 7-H).

Anal. Calculated for  $C_{12}H_{18}O$ : C, 80.90; H, 10.11. Found: C, 80.69; H, 10.12.

In an alternate procedure 0.100 g of XL in 1 ml of dry pyridine was treated with 0.12 ml of phosphorus oxychloride at room temperature. The solution was allowed to stand at room temperature for 18 hours, water was added and the reaction was worked up as described above. Spectral analysis of the recovered material showed that no reaction had taken place.

In another method carboxysulfamoyl triethyl ammonium hydroxide inner salt, methyl ester was prepared according to the procedure of Burgess, Penton, and Taylor (20). To a solution of 0.85 g (0.0036 mole) of inner salt in 2 ml of dry acetonitrile stirred under nitrogen was added 0.226 g (0.00115 mole) of XL in 1.5 ml of acetonitrile. The solution was stirred at 40°C for 75 minutes, cooled to room temperature, and 5 ml of water was added. The mixture was extracted with 30 ml of ether, the extracts were washed with brine and dried, and the solvents were removed to afford 0.196 g (96 percent) of an oil which was shown by nmr analysis to be a 2:1 mixture of the desired ketone XLI and ketone LIX with the exocyclic double bond. The nmr spectrum of the mixture showed the two vinyl hydrogens in LIX at  $\delta$  4.55 and 4.85. No isomerization of LIX into XLI occurred on distillation or on chromatography on silica gel or on acid alumina, and the mixture of products could not be separated by these procedures. Treatment of a solution of LIX in carbon tetrachloride in an nmr tube with 0.1 ml of tri-

fluoroacetic acid for two days at room temperature partially isomerized the double bond and resulted in a 10:1 mixture of compounds XLI and LIX, as determined by nmr analysis.

2-Hydroxy-2-isopropenyl-6,10 $\alpha$ -dimethyl[4.5]spirodecene-6 (XLII)

In a 25 ml round-bottom flask under nitrogen a mixture of 0.247 g (0.0102 mole) of magnesium, 8 ml of dry tetrahydrofuran (freshly distilled from lithium aluminum hydride), and a crystal of iodine was stirred at room temperature. To the mixture three drops of carbon tetrachloride were added, and 1.505 g (0.0124 mole) of freshly distilled isopropenyl bromide was added dropwise at such a rate that the temperature of the reaction mixture stayed at about 40°C. After addition was complete the mixture was stirred at room temperature for five hours and was then cooled to 5°C in an ice bath. A solution of 0.145 g (0.00081 mole) of XLI in 3 ml of dry tetrahydrofuran was added dropwise, and the mixture was stirred at 15-20°C for 1.25 hours. Then 20 ml of aqueous ammonium chloride was added, the mixture was extracted with 20 ml of ether, and the ether extracts were washed with 2 percent sodium bicarbonate and water and dried. The ether was removed in vacuo, and the residue was chromatographed on silica gel using hexane-ether as eluent. Elution with 3 percent ether in hexane yielded 0.058 g (37 percent) of a mixture of isomers of XLII and further elution with the same solvent gave 0.019 g of starting material. The mixture showed the following spectral properties: ir (film) 3450 (OH), 1638 (C=C), 1450, 1376, 898 and 800 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>)  $\delta$  0.90 and 1.00 (2d, J = 6.5 Hz, 3H, 10-CH<sub>3</sub>'s), 1.65 and 1.78 (2d, J = 1.5 Hz,

3H, 6-CH<sub>3</sub>'s), 1.83 (d, J = 0.5 Hz, 3H, isopropenyl CH<sub>3</sub>), 4.73 (m, 1H, isopropenyl =CH<sub>2</sub>), 4.99 (q, J = 0.5, 1H, isopropenyl =CH<sub>2</sub>), and 5.26 (s, w<sub>h</sub> = 8 Hz, 1H, 7-H); mass spectrum (70 eV) m/e 220 (M<sup>+</sup>), 202 (M<sup>+</sup>-H<sub>2</sub>O), 187 (M<sup>+</sup>-H<sub>2</sub>O, CH<sub>3</sub>), and 178 (M<sup>+</sup>-CH<sub>3</sub>CH=CH<sub>2</sub>).

#### α-Vetispiene (XXXIII)

A solution of 0.088 g (0.0004 mole) of XLIII in 2 ml of dry pyridine was placed in a 10 ml round-bottom flask under nitrogen and was cooled to 0°C in an ice-salt bath. The solution was treated with 0.092 ml of thionyl chloride dropwise so that the temperature remained close to -5°C. After the addition was complete the solution was stirred at -10 to -5°C for 35 minutes, and 5 ml of water was added dropwise keeping the temperature of the mixture about 0°C. The mixture was extracted well with 30 ml of ether, the extracts were washed with brine and dried, and the ether was removed to leave 0.065 g of crude XXXIII. Chromatography on silica gel using hexane-ether as eluent afforded 0.007 g (10 percent) of α-vetispiene (hexane) with spectral data consistent with those of the natural product: uv max (95 percent EtOH) 238 nm; ir (film) 1630, 1600, 1450, 1378 and 880 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>) δ 0.86 (d, J = 6 Hz, 3H, 10-CH<sub>3</sub>), 1.54 (d, J = 2 Hz, 3H, 6-CH<sub>3</sub>), 1.91 (d, J = 1 Hz, 3H, isopropenyl CH<sub>3</sub>), 4.86 (s, 2H, C = CH<sub>2</sub>), 5.33 (m, 1H, 7-H), and 5.46 (s, 1H, 1-H); mass spectrum (70 eV) m/e 202 (M<sup>+</sup>), 187 (M<sup>+</sup>-CH<sub>3</sub>), 160 (M<sup>+</sup>-CH<sub>3</sub>CH=CH<sub>2</sub>), and 145 (M<sup>+</sup>-CH<sub>3</sub>, CH<sub>3</sub>CH=CH<sub>2</sub>).

In an alternate procedure, the dehydration was attempted using



carboxysulfamoyl triethyl ammonium hydroxide inner salt, methyl ester (20). Treatment of 0.075 g of XLII with 0.3 g of inner salt in 3 ml of acetonitrile at 0°C for two hours yielded on normal workup only the starting material. At 15°C for two hours there was also no reaction, and at 30°C no identifiable products were isolated.

In a third attempt at dehydration 0.058 g of XLIII was refluxed in 10 ml of benzene with a small crystal of iodine for two hours. The solvent was removed in vacuo, 10 ml each of ether and aqueous sodium bicarbonate were added to the dark residue, and solid sodium bisulfite was added to destroy the excess iodine. The layers were separated, the aqueous layer was extracted with 10 ml of ether, and the organic layers were washed and dried. Removal of the solvent in vacuo yielded no identifiable product, but showed the disappearance of the terminal methylene group.

2-Hydroxy-2-ethynyl-6,10 $\alpha$ -dimethyl[4.5]spirodecene-6 (XLIII)

Following the procedure of Křiž, Beneš, and Peška (21), 0.040 g of a 53 percent sodium hydride-oil dispersion (0.00087 mole) was placed in a 10 ml three-neck round-bottom flask equipped with a magnetic stirrer and gas dispersion tube and maintained under a nitrogen atmosphere. The dispersion was washed twice with 5 ml of hexane to remove the oil, and 3 ml of dry dimethylsulfoxide (distilled from sodium hydride and stored over molecular sieves) was added. The mixture was warmed to 70°C for 30 minutes with vigorous stirring and was then cooled to room temperature. Acetylene was passed through the reaction mixture for 30 minutes to give a clear

black solution, and 0.046 g (0.00026 mole) of ketone XII in 5 ml of dry tetrahydrofuran was added dropwise over 30 minutes while acetylene was continuously passed through the solution. The reaction mixture was stirred for five hours, after which time the flow of acetylene was discontinued and 0.1 g of solid ammonium chloride was added. The mixture was filtered, and the solvents were removed by lyophilization. The residue was dissolved in 5 ml each of ether and water, the layers were separated, and the aqueous layer was extracted with 5 ml of ether. The combined ether layers were washed and dried, and the solvent was removed in vacuo to afford 0.057 g of a crude mixture of ethynyl carbinols XLIII with the following spectral properties: ir (film) 3380 (OH), 1628, 1450, 1375 and 1163  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  0.90 and 0.96 (2d,  $J = 6$  Hz, 3H, 10- $\text{CH}_3$ 's), 1.59 (d,  $J = 1.5$  Hz, 3H, 6- $\text{CH}_3$ ), and 5.32 (s,  $w_h = 8$  Hz, 1H, 7-H).

2-Acetoxy-2-acetyl-6,10 $\alpha$ -dimethyl[4.5]spirodecene-6 (XLIV)

In accordance with the procedure of Jacques (22), a mixture of 0.035 g of the crude ethynyl carbinol XLIII and 0.070 g of mercuric acetate in 4 ml of ethyl acetate was stirred at room temperature for 24 hours under a nitrogen atmosphere. Then with stirring continued, hydrogen sulfide was bubbled through the solution for 10 minutes, and the black precipitate which formed was removed by filtration through celite. Removal of the solvent in vacuo gave 0.026 g of crude XLIV: ir (film) 1736 (ester  $\text{C}=\text{O}$ ), 1719 (methyl  $\text{C}=\text{O}$ ), 1635, 1456, 1378, 1259, 1167 and 788  $\text{cm}^{-1}$ ; nmr ( $\text{CCl}_4$ )  $\delta$  0.89 and 0.94 (2d,  $J = 6$  Hz, 3H, 10- $\text{CH}_3$ 's), 1.68 (6- $\text{CH}_3$ ), 2.03 (s, 3H, 2-OAc),

2.06 and 2.08 (2s, 3H, 2-COCH<sub>3</sub>'s), and 5.33 (s, 1H, 7-H).

2-Acetyl-6,10 $\alpha$ -dimethyl[4.5]spirodecene-6 (XLVI)

Following a procedure derived from that reported by Chapman (23), 25 ml three-neck round-bottom flask was fitted with a dry ice condenser, mechanical stirrer, and gas inlet and outlet tubes, and in it 10 ml of ammonia (freshly distilled from lithium) was collected. A solution of 0.040 g of the crude product from above in 5 ml of dry dioxane was added, and then 0.029 g of calcium was added in small pieces. The mixture was stirred at reflux for one hour and was then filtered through glass wool into a flask containing 0.1 g of ammonium chloride. The solvents were removed, and the residue was taken up in 10 ml each of ether and water. The ether layer was separated, dried, and concentrated to give an oil (XLV) which was dissolved in 3 ml of acetone and titrated with Jones reagent (24) until the color persisted. One drop of isopropyl alcohol was added and the reaction mixture was filtered. Removal of the solvents in vacuo left 0.023 g of an oil which appeared to contain the desired product XLVI: ir (film) 1709 (methyl C=O), 1459, 1378, 1367 and 790 cm<sup>-1</sup>; nmr (CCl<sub>4</sub>)  $\delta$  0.86 and 0.90 (2d, J = 6.5 Hz, 3H, 10-CH<sub>3</sub>'s), 1.66 and 1.67 (2d, J = 1.5 Hz, 3H, 6-CH<sub>3</sub>), 2.06 (s, 3H, 2-COCH<sub>3</sub>), and 5.26 (s, 1H, 7-H).

## CHAPTER IV

## DISCUSSION OF RESULTS

The principal goal of this research, as stated in the first chapter, was to carry out the synthesis of racemic  $\alpha$ -vetispiene, a sesquiterpene triene. Various changes and improvements in the method of attack of this problem over methods used in syntheses of other compounds with the same carbon skeleton will be discussed.

As was previously mentioned, the synthetic method employed by Marshall in the syntheses of hinesol, agarospirol, and  $\beta$ -vetivone involved the rearrangement of a cross-conjugated cyclohexadienone XI to give a spiro ketone XII (11). From here it was necessary to introduce a new functionality at C-2 and remove the C-3 carbonyl in order to make the natural products. Less than desirable yields for the rearrangement (39 percent) and transposition of functional group (36 percent) prompted attempts at an improved synthesis of vetispiranes.

The route chosen again involved the photochemical rearrangement of a 6/6-fused cross-conjugated cyclohexadienone as the key step. However, it seemed desirable to have a functional group present at C-2 in the dienone. The enone XXXIV was prepared in four steps according to the method of Caine and Tuller by alkylation of 2,6-dimethylcyclohexanone with 1,3-dichloro-2-butene, dehydrohalogenation of the resulting vinyl chloride and shift of the triple bond to give

a terminal acetylene, hydration of the triple bond, and finally base catalyzed closure of the A ring (25). It has been found that

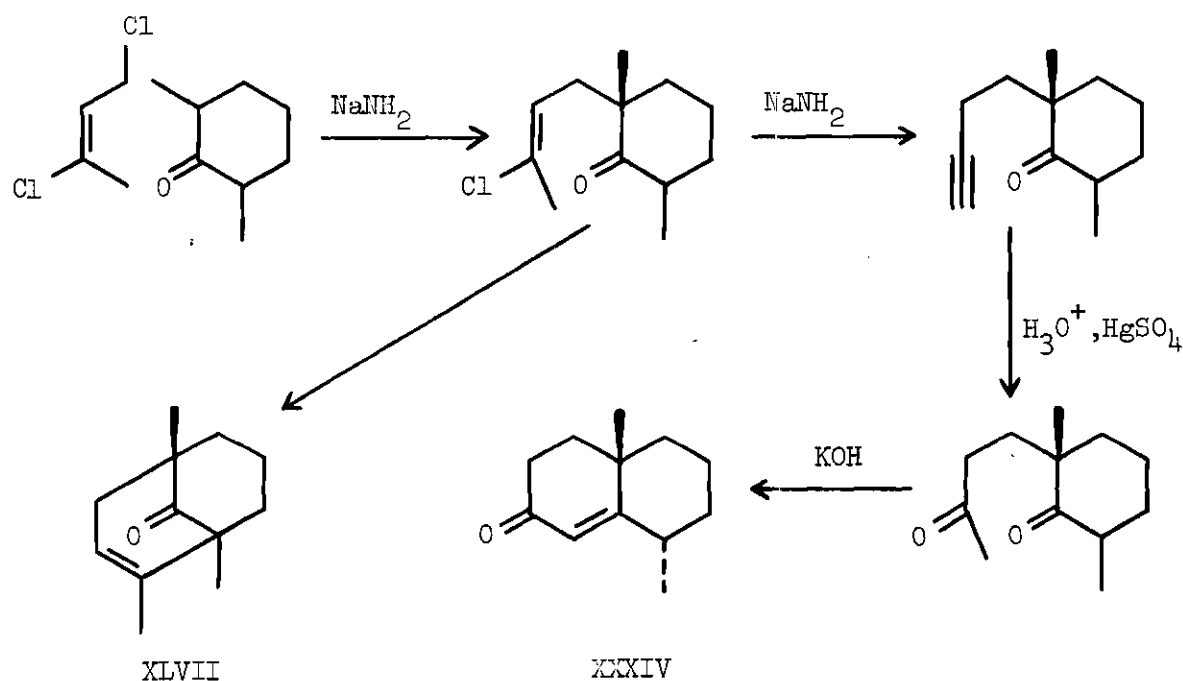


Chart VIII. Synthesis of 3-Keto-6,10-dimethyl- $\Delta^4$ -octahydronaphthalene.

direct acid hydrolysis of the vinyl chloride results in formation of enone XLVII and none of the desired enone (26). The 6-methyl group in XXXIV is at an epimerizable position and therefore exists in the more stable equatorial configuration trans to the 10-methyl group.

The desired 2-methoxy dienone XXXV was prepared in three steps from the enone. Acetoxylation with lead tetraacetate by the procedure of Seebach (27) gave the  $\alpha$ -acetoxy enone XLVIII which was accompanied

by some of the dienone XLIX arising from elimination of acetic acid. Hydrolysis of the acetate and air oxidation led to the hydroxy dienone L which was methylated with potassium *t*-butoxide and methyl iodide to give XXXV. These three steps were straightforward and the dienone was isolated in 15 percent yield from the enone XXXIV (19).

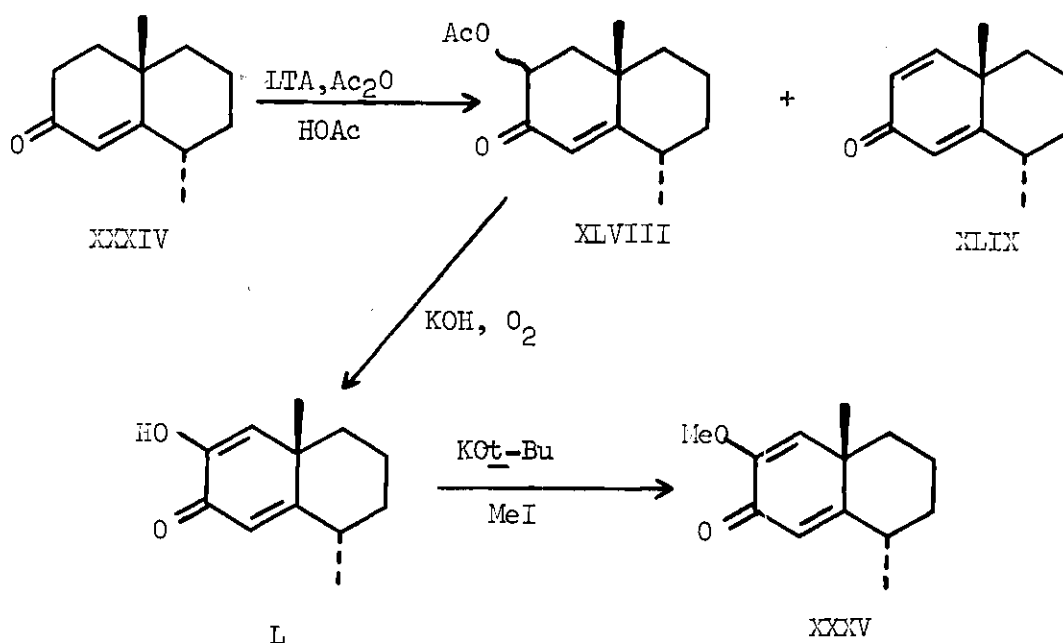


Chart IX. Synthesis of 2-Methoxy-3-keto-6,10-dimethyl- $\Delta^{1,4}$ -hexahydronaphthalene.

This 2-methoxy dienone seemed to be well suited for the purpose of conversion to a [4.5]spiro precursor of  $\alpha$ -vetispiene. First the 6- and 10-methyl groups had the required trans stereochemistry (see Chapter I). Also the electron donating methoxyl

group at C-2 would stabilize the proposed intermediate LI and aid in the rearrangement of the dienone to a spiro system. Finally the enol ether function can be easily hydrolyzed to the ketone, providing a facile method for introduction of the isopropenyl side chain of the natural product.

Irradiation of the dienone XXXV in glacial acetic acid did indeed give the expected [4.5]spiro acetoxyl ketone XXXVI. The product showed ir absorptions at 1720, 1710, and 1626  $\text{cm}^{-1}$  for the ester carbonyl, the  $\alpha,\beta$ -unsaturated carbonyl in the five-membered ring, and the conjugated double bond, respectively. Other evidence confirming XXXVI as the product are nmr absorptions 2.03, 3.77 and 6.22 ppm indicating the presence of acetoxyl and methoxyl groups and a vinyl proton on a conjugated system. Finally the mass spectrum and C,H analysis confirmed the formula. The stereochemistry of the 6-methyl group remains the same in the product, and the stereochemistry at the other two asymmetric centers has been determined from rearrangements of related dienones (see Chapter I). The yield in this rearrangement was about 90 percent which was almost three times the yield of the hydroxy ketone LII produced in the photolysis of XXXV in aqueous acetic acid. This rearrangement had been carried out by Dawson, and the lower yield was thought to be due to partial hydrolysis of the enol ether in the aqueous acid (19). So the rearrangement in glacial acetic acid represents a major improvement in yield over the rearrangements of both Marshall (see Chapter I) and Dawson.

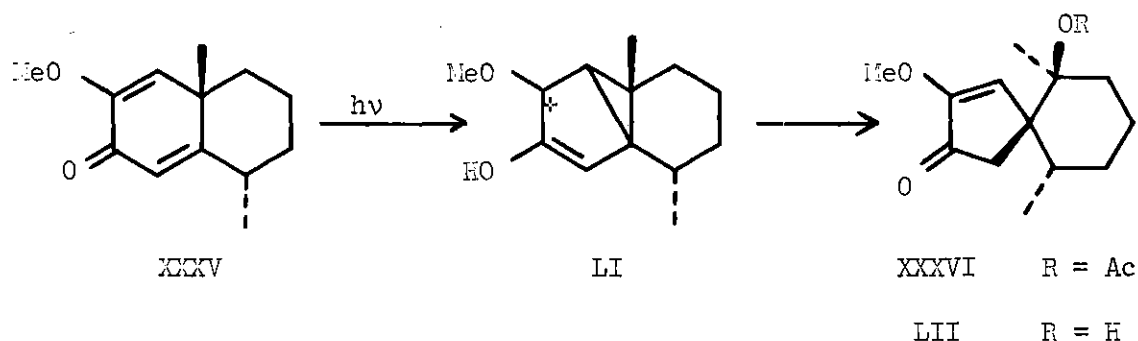


Chart X. Photolysis of the 2-Methoxy Dienone.

The next problem in the synthesis was the conversion of the photoproduct into the ketone intermediate XLI. A synthesis of XLI from LII in five steps has been developed by Dawson using standard reactions (19). The hydroxy ketone was first dehydrated on treatment with thionyl chloride in pyridine, but the product was isolated in only about 30 percent yield. Sodium borohydride reduction of the carbonyl and acetylation of the resulting alcohols led to the acetates LIII in good yield. The acetate function was removed on reduction with lithium in ethylamine, and ketone XLI was produced finally on hydrolysis of the enol ether in aqueous oxalic acid. The overall yield for this conversion was only about 30 percent, (see Chart XI).

In the present work an attempt at an improvement in this conversion was made using the same steps, but applying them in somewhat different order and starting with the acetoxo ketone rather than with the hydroxy ketone. The photoproduct XXXVI was first reduced to the hydroxy acetates XXXVII in quantitative yield.



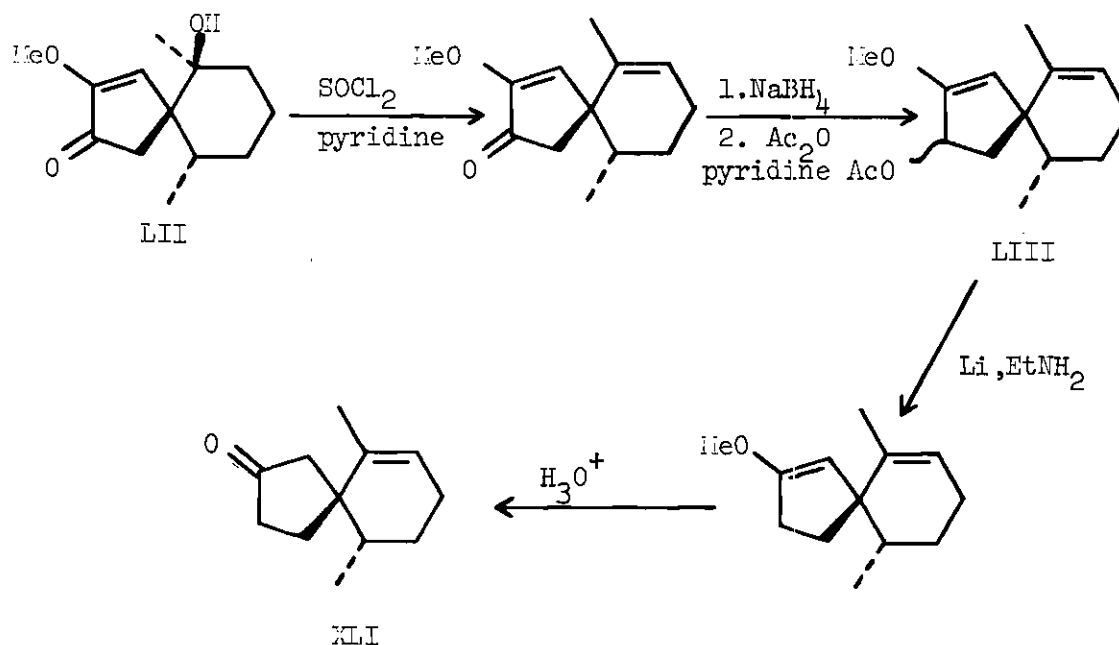


Chart XI. Synthesis of the Intermediate Ketone by Dawson.

A broad melting point range (80-90°C) and two sets of nmr absorptions for the methyl, acetoxy, and methoxyl groups and for the vinyl hydrogen indicated that both C-3 epimers had been produced. There was an nmr absorption (doublet of doublets) at 4.57 ppm for the 3-hydrogen being split by the two C-4 hydrogens and ir absorptions at 3420, 1725, and 1648  $\text{cm}^{-1}$  for the hydroxyl group, the ester carbonyl, and the double bond.

Acetylation with acetic anhydride in pyridine gave the diacetates XXXVIII in good yield. The ir absorptions at 1730 and 1650  $\text{cm}^{-1}$ , the presence of a second acetoxy absorption in the nmr spectrum, and C,H analysis confirmed the structure of the product, (see Chart XII).

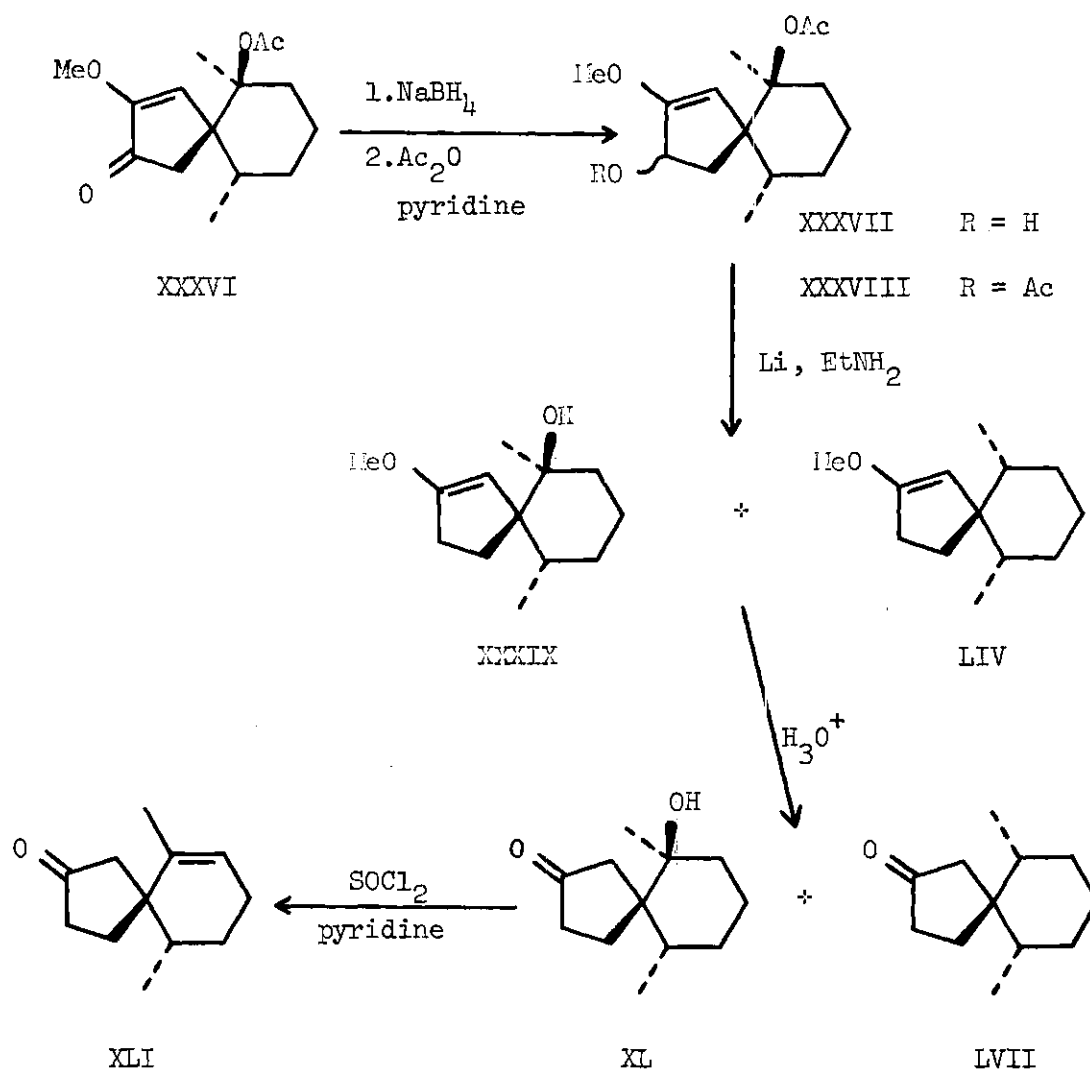


Chart XII. Synthesis of the Intermediate Ketone.

The third step, removal of the secondary acetate accompanied by reduction of the tertiary acetate to an alcohol, did not proceed as smoothly as was desired. The reaction with lithium in ethylamine containing an equivalent of *t*-butyl alcohol as a proton source proceeded readily at  $-78^{\circ}\text{C}$ . The lithium reacted as soon as it dissolved, and the reaction was stopped shortly after the mixture turned blue indicating an excess of lithium and solvated electrons in the solution. Although products from this reaction were not separated after this step, nmr and glc analysis indicated that the product was actually a 2:1 mixture of the desired alcohol XXXIX and the product LIV arising from complete removal of the tertiary acetate. These assignments were confirmed on separation of the products after the next step. Varying the amount of *t*-butyl alcohol present or varying the time of reaction after the blue color persisted did not affect the yield of either product. Spectra of the mixture showed the presence of a hydroxyl group and the enol ether. The 10-methyl group of XXXIX and both methyl groups of XLIV give an nmr doublet at 0.78 ppm, so this absorption is significantly larger than the singlet at 1.09 ppm for the 6-methyl group of XXXIX.

The accepted mechanism for the metal-amine reduction of an acetate to an alcohol consists of four steps: addition of an electron to the carbonyl, protonation of the radical anion, addition of a second electron, and elimination of the alkoxide anion (28), (see Chart XIII). The reduction of an allyl acetate to a methylene group proceeds in three steps: addition of an electron to the

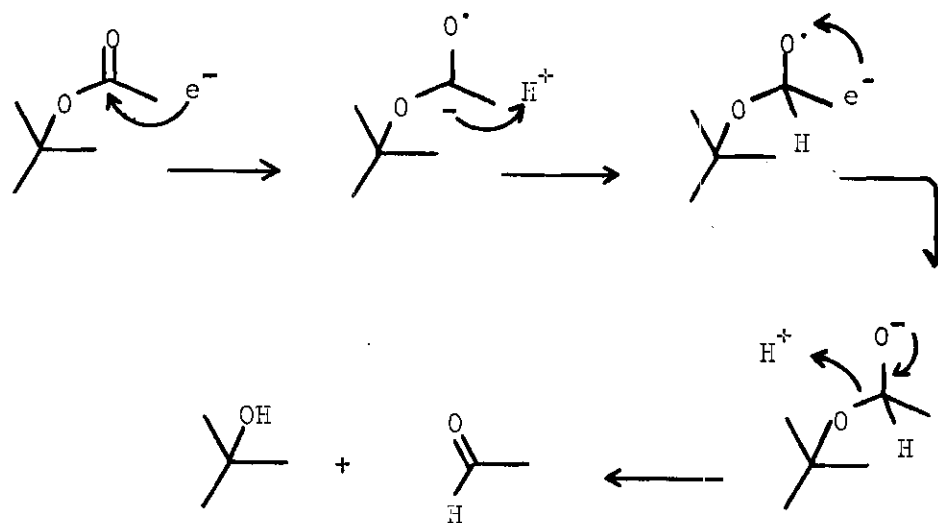


Chart XIII. Mechanism for the Metal-Amine Reduction of an Acetate to an Alcohol.

double bond and elimination of the acetate, addition of a second electron, and protonation of the allylic anion (28).

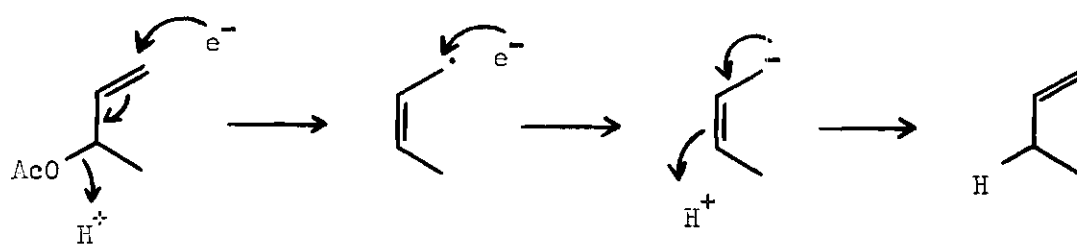
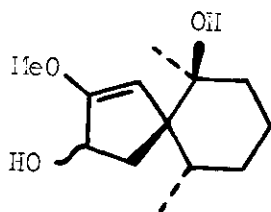


Chart XIV. Mechanism for the Metal-Amine Reduction of an Allyl Acetate to a Methylene Group.

Since none of the diol LV was found to be present after this reaction, it appears that, given a choice of these two mechanistic

pathways, the second will be followed leading to complete removal of the acetate. For this reason and after examining the stereochemistry



LV

of the diacetate, it is now proposed that the elimination of the tertiary acetate proceeds by a mechanism analogous to that for the reduction of an allyl acetate. Addition of an electron to the double bond could be followed by displacement of the acetoxyl group to form a three-membered ring intermediate. Addition of the second electron leads to opening of the three-membered ring to give LVI in which R is a hydrogen or an acetoxyl group depending on which acetoxyl group is reduced first. There is an obvious similarity between the cyclopropyl intermediate in the reduction and the cyclopropyl intermediate in the photochemical rearrangement LI, (see Chart XV).

In the next step of the synthesis the crude mixture of the two enol ethers XXXIX and LIV was treated with aqueous oxalic acid, and the ketones XL and LVII were isolated in about 45 percent and 30 percent yield, respectively, from the diacetate. Spectra of XL showed the presence of a hydroxyl group and a saturated carbonyl group in a five-membered ring. At this point it was verified from the nmr

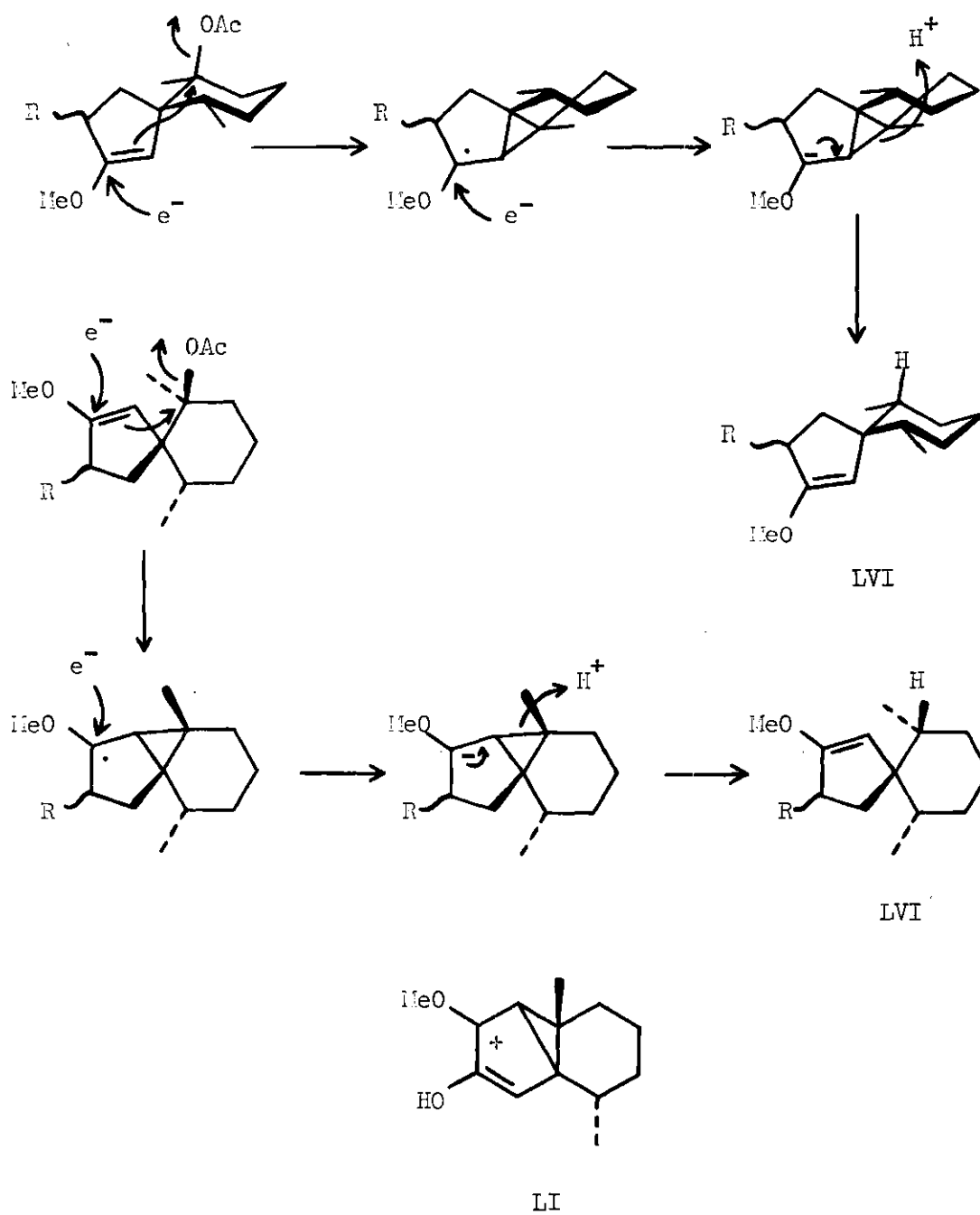
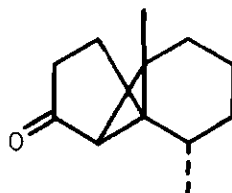


Chart XV. Mechanism for the Metal-Amine Reduction of the Spiro Acetate.

spectrum of LVII that the methyl groups give a single six proton doublet and are therefore equivalent and oriented cis to each other on the six-membered ring. This compound had been previously prepared by Chao by lithium-ammonia reduction of the tricyclic ketone LVIII (29).



LVIII

Dehydration of the hydroxy ketone XL with thionyl chloride in pyridine gave the desired ketone XLI in relatively low yield when the reaction was kept at  $5-10^{\circ}\text{C}$ . However, when care was taken to keep the temperature at  $0^{\circ}\text{C}$  a yield of 60 percent was obtained approximately doubling that achieved by Dawson in the dehydration of LII (19). No other product was isolated after this reaction. There was apparently a water-soluble complex formed which did not break up to give either product or starting material and so was not extracted from the aqueous solution in the workup. The ir spectrum of the product again showed an absorption for the saturated carbonyl in a five-membered ring at  $1742\text{ cm}^{-1}$ , and the nmr spectrum indicated the presence of secondary and vinyl methyl groups and a vinyl hydrogen with absorptions at 0.90, 1.65, and 5.37 ppm, respectively.

Attempts were made to increase the yield using other dehydrating agents. With phosphorous oxychloride in pyridine at room temperature there was no reaction after 24 hours, and all of the starting material

was recovered. Using carboxysulfamoyl triethyl ammonium hydroxide inner salt, methyl ester (20) an almost quantitative yield of dehydrated product was obtained after reaction for 75 minutes at 40°C, but the product was found by nmr analysis to be a mixture of endo-cyclic and exocyclic double bond isomers.

The exocyclic double bond isomer LIX is apparently produced in the inner salt dehydration since this reaction proceeds by a cis elimination mechanism. Since the stereochemistry of the hydroxy ketone XL is such that the  $\beta$ -hydrogen H<sub>1</sub> (see Chart XVI) is not exactly cis to the hydroxyl group, there is some tendency to pull off a methyl hydrogen H<sub>2</sub> which can be oriented cis to the hydroxyl group, thus forming the less stable double bond isomer. The thionyl chloride dehydration, of course, involves a trans elimination, and the trans methylene hydrogen H<sub>3</sub> is removed by the pyridine before a methyl hydrogen which has to attain the correct orientation first, (see Chart XVI).

All attempts to separate the isomers by distillation, column chromatography, and gas chromatography were unsuccessful. Partial isomerization of the double bond into the ring took place on treatment of the mixture with trifluoroacetic acid. Thus the 65 percent endo mixture gave a 90 percent endo mixture after acid treatment. As Dawson had previously discovered, this spiro system was also found to be labile to acid catalyzed rearrangement to the 6/6-fused enone XXXIV (19). Acid treatment in some cases resulted in total conversion to XXXIV via the intermediate LX with the methyl groups cis.



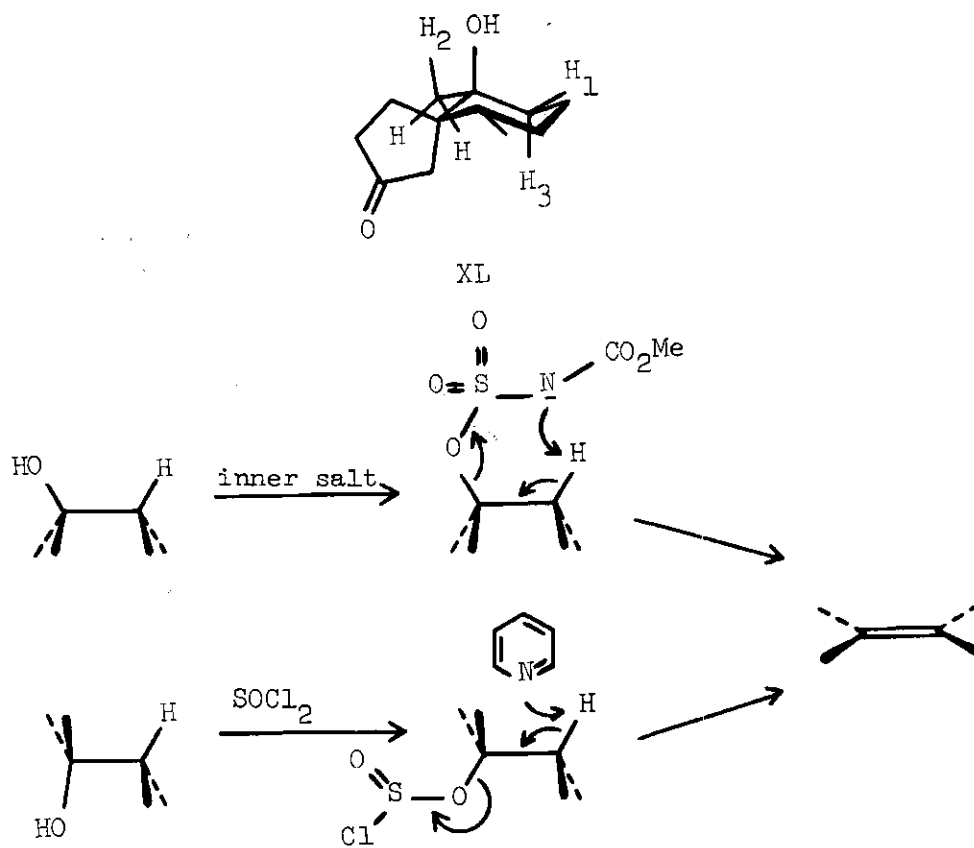


Chart XVI. Mechanisms of Thionyl Chloride and Inner Salt Dehydrations.

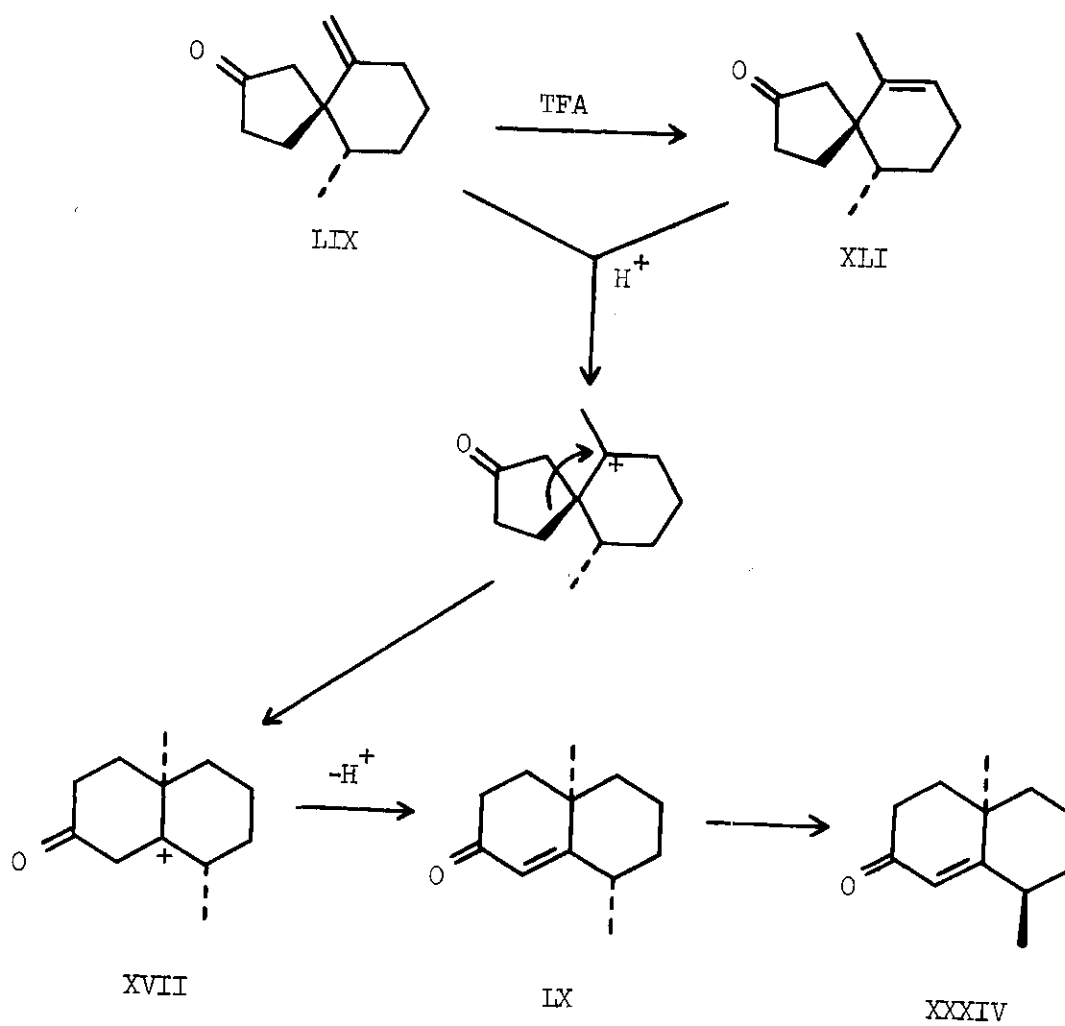


Chart XVII. Acid Catalyzed Rearrangements of Spiro Enones.

So thionyl chloride remained the reagent giving the best yield of pure XLI. This ketone was produced in an overall yield of 19 percent from the methoxy dienone XXXV. This improved synthetic route more than doubles the 8 percent overall yield obtained in Dawson's synthesis and represents a distinct improvement in the 14 percent yield of XIV from XI obtained by Marshall.

In order to complete the synthesis of the natural product, it was necessary to introduce an isopropenyl group into the molecule at C-2. To this end isopropenyl magnesium bromide was prepared and reacted with the enone XLI. Both C-2 epimers of the allylic alcohol XLII were formed, and they showed two new absorptions at 4.73 and 4.99 ppm in the vinyl region of the nmr spectrum for the two terminal methylene hydrogens. A new absorption for the isopropenyl methyl group was also present as well as two sets of doublets for the 6- and 10-methyl groups and a 5.26 ppm peak for the 7-hydrogen. Further confirmation of the presence of XLII were mass spectrum peaks for the molecular ion and for a dehydrated species.

Dehydration, again using thionyl chloride at 0°C, gave racemic  $\alpha$ -vetispiene (XXXIII). The nmr spectrum of this compound showed only one absorption at 4.85 ppm for the two methylene vinyl hydrogens with absorptions for the remaining two vinyl hydrogens at 5.36 and 5.45 ppm. The glc spectrum showed the presence of one pure compound, and except for a single nmr peak at 1.25 ppm for a nonvolatile impurity, the nmr, ir, and uv spectra were identical to those of natural  $\alpha$ -vetispiene which were kindly supplied by Professor Andersen. A

sample of authentic  $\alpha$ -vetispiene was not available for comparison.

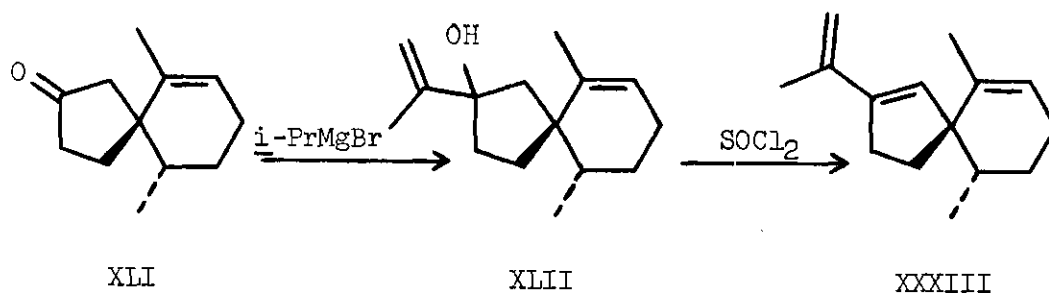
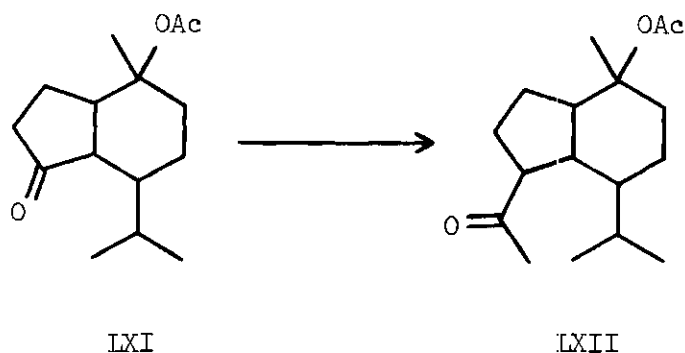


Chart XVIII. Synthetic Route to  $\alpha$ -Vetispiene.

Some work was also done on the conversion of XLI into the methyl ketone XLVI. Since this compound was an intermediate in Marshall's syntheses of hinesol, agarospirol, and  $\beta$ -vetivone (11), completion of this conversion would constitute a formal total synthesis of these three natural products. Attempts by Dawson to add lithium acetylide, sodium acetylide, and lithium acetylide-ethylenediamine complex to the enone had been unsuccessful (19). However, following a synthetic route used by Tuller in the conversion of LXI to oplopanone (LXII), better results were obtained (30).



First, in a procedure developed by Křiž, Beneš, and Peška (21) sodium acetylide, formed using dimethyl sodium, was added to XLI to give the ethynyl carbinol XLIII. The crude product was then treated with mercuric acetate in ethyl acetate and in turn with hydrogen sulfide after the method of Jacques (22) to hydrate the triple bond and make the tertiary acetate XLIV. Finally the acetate was removed on reduction with calcium in liquid ammonia, and the ketone which was also reduced in the reaction was regenerated using Jones reagent.

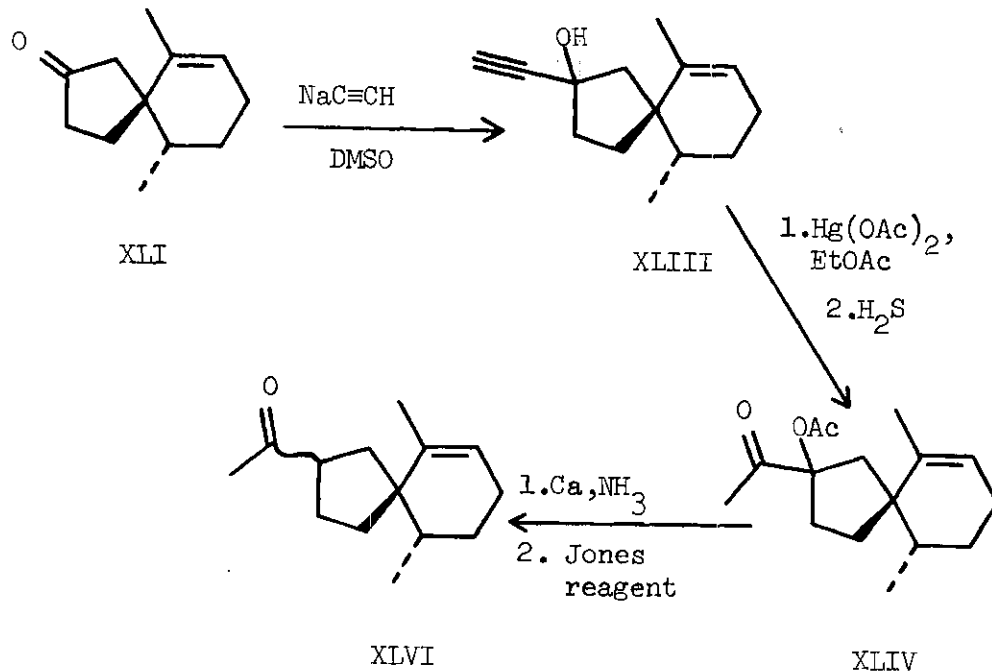


Chart XIX. Synthetic Route to the Methyl Ketone.

Spectral analysis showed that some of the desired methyl ketone

was present in the product, but the amount of material available did not allow complete purification and characterization of the products in this preliminary work.

## CHAPTER V

## CONCLUSIONS

The 6/6-fused cross-conjugated cyclohexadienone XXXV was prepared and irradiated in glacial acetic acid. The resulting rearrangement to the spiro acetoxy ketone XXXVI was consistent with those of previously reported systems containing an electron releasing substituent at C-2.

A synthetic route was developed for the conversion of the photoproduct into the spiro ketone XLI which can be used as an intermediate in the syntheses of a number of compounds related to  $\beta$ -vetivone. One of these compounds,  $\alpha$ -vetispiorene (XXXIII) was synthesized using the intermediate ketone XLI, and preliminary work was done on the synthesis of the methyl ketone XLVI, the completion of which would constitute a total synthesis of three more natural products, (see Chart XX).

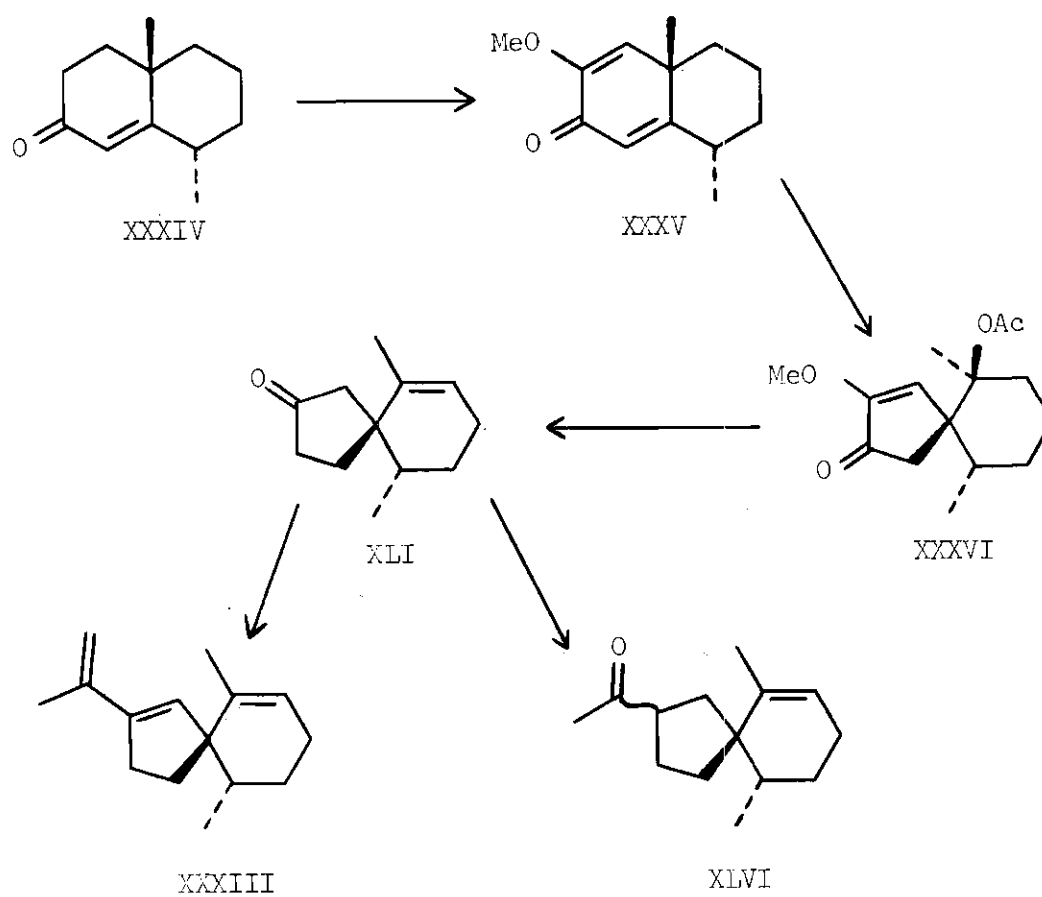


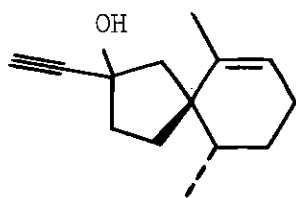
Chart XX. Summary of Work.



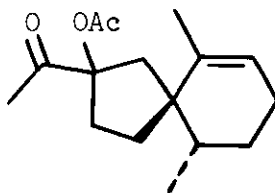
## CHAPTER VI

## RECOMMENDATIONS

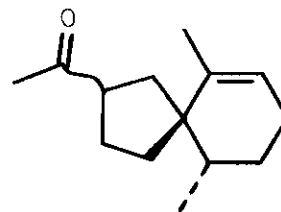
The synthesis of the methyl ketone should be completed, and spectral data and analyses should be obtained on compounds XLIII and XLIV.



XLIII

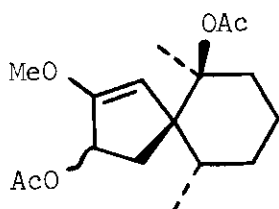


XLIV

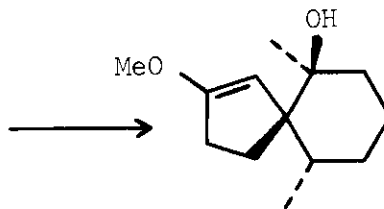


XLVI

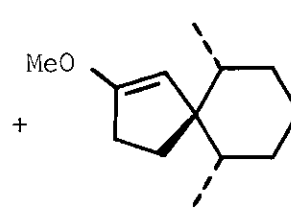
The lithium-ethylamine reduction of the diacetate XXXVIII should be studied, and attempts should be made to increase the yield of the desired alcohol XXXIX while minimizing the production of LIV. If better conditions or reagents cannot be found to improve the



XXXVIII



XXXIX



LIV

reaction, a possible modification of the synthetic route from the photoproduct XXXVI to ketone XLI should be considered. One possible alternate route is shown in Chart XXI.

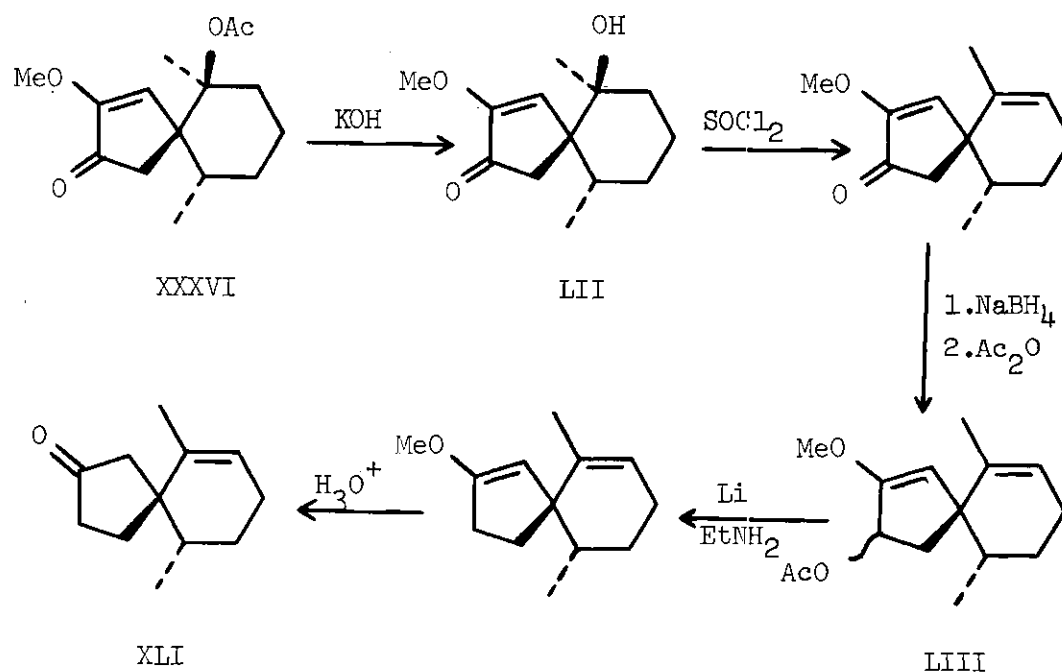


Chart XXI. Alternate Route to the Intermediate Ketone.

Also the possibility of rearranging the trienone LXIII to the tricyclic intermediate LXIV should be further investigated. If the rearrangement of this heretofore photostable trienone could be induced, either by use of a sensitizer or through a more photolabile, substituted trienone, the intermediate ketone XLI could be easily obtained in the manner shown in Chart XXII.

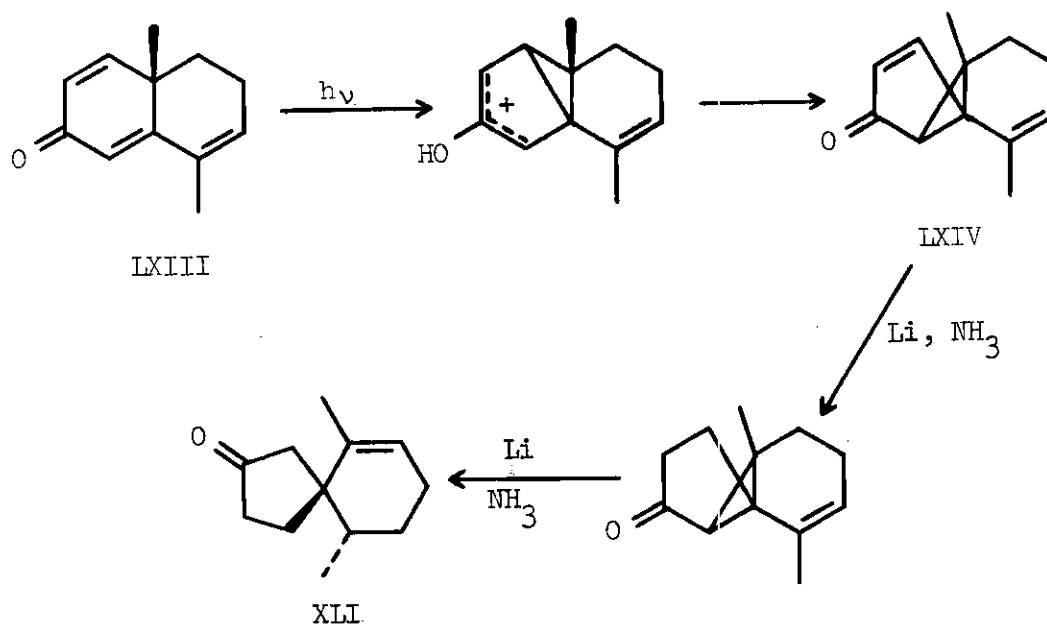


Chart XXII. Possible Short Route to the Intermediate Ketone.

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## VITA

Paul Fredric Ingwalson, son of Dr. and Mrs. Raymond W. Ingwalson, was born in Rockford, Illinois, on April 29, 1945.

He attended elementary and secondary schools in Gainesville, Florida, and Chattanooga, Tennessee, and was graduated from Brainerd High School, Chattanooga, Tennessee, in 1963. He received his Bachelor of Science Degree in Chemistry in 1967 from Wittenberg University, Springfield, Ohio. In June, 1967, he began graduate work in the School of Chemistry at the Georgia Institute of Technology, Atlanta, Georgia.

He is a member of the American Chemical Society. He is married to the former Grace Ann Milligan and has one daughter, Katherine Rebecca.